A new class of chiral sulphoxides for asymmetric synthesis

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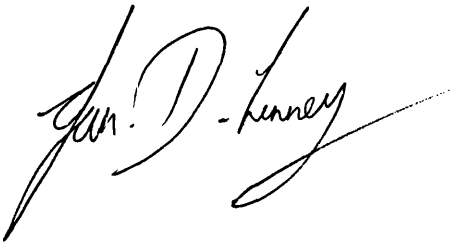
A NEW CLASS OF CHIRAL SULPHOXIDES FOR ASYMMETRIC SYNTHESIS

submitted by Ian Duncan Linney
for the degree of PhD
of the University of Bath
1993.



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Lastly, thank you to mum and dad, and of course to my wife, Lynda.

ABBREVIATIONS

Å	Angstrom
Ac	acetyl
aq	aqueous
n-Bu	$(CH_2)_3CH_3$
t-Bu	$C(CH_3)_3$
d.e	diastereoisomeric excess
4-DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
D_2O	deuterium oxide
e.e	enantiomeric excess
Et	CH_2CH_3
F.A.B.	Fast Atom Bombardment
F.C.	Flash Chromatography
H.P.L.C.	High Performance Liquid Chromatography
L. D. A.	lithium disopropylamide
m/z	mass charge ratio
MgBrDA	magnesium bromide diisopropylamide
M. p.	melting point
Me	CH_3
NaHMDS	sodium hexamethyldisilylamide
Nuc	nucleophile
Ph	phenyl
n-Pr	$(CH_2)_2CH_3$
i-Pr	$(CH)(CH_3)_2$
t.l.c.	thin layer chromatography
p-Tol	$4\text{-}MeC_6H_4$

NMR spectroscopy

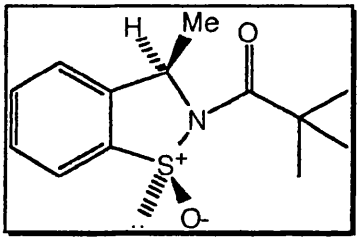
^{1}H	proton
^{13}C	carbon
J	coupling constant in Hertz
s	singlet
d	doublet
t	triplet
q	quartet
b	broad

INDEX

SUMMARY

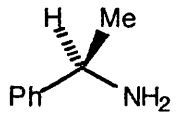
The synthesis and utility of a new source of chiral sulphoxide which has the potential to be regenerated will be described within this thesis.

Cyclic sulphinamide (**I**) was chosen as the substrate for the sulphoxide source.

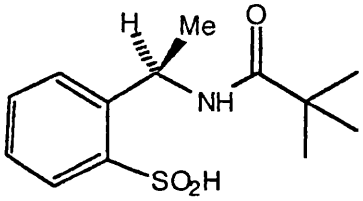


(**I**)

Sulphinamide (**I**) was synthesised from commercially available (R)-(+)-(**II**) in three steps, in 54% chemical yield. Treatment of acid (**III**) with thionyl chloride and 4-dimethylaminopyridine induced the required diastereoselective cyclisation to *cis*-(**I**).

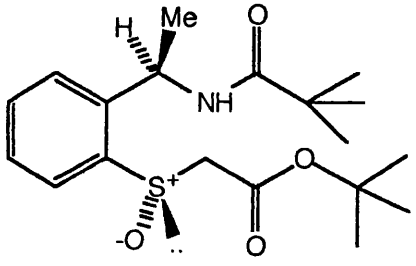


(R)-(+)-(**II**)

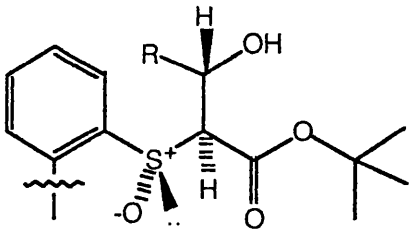


(**III**)

Reaction of (**I**) with the enolate of *tert*-butyl acetate resulted in the formation of sulphinyl acetate (**IV**). Subsequent reactions of the enolate of (**IV**) with aldehydes resulted in the formation of adducts (**V**) of varying diastereoisomeric selectivity generated *via* a thermodynamic, equilibrating pathway.

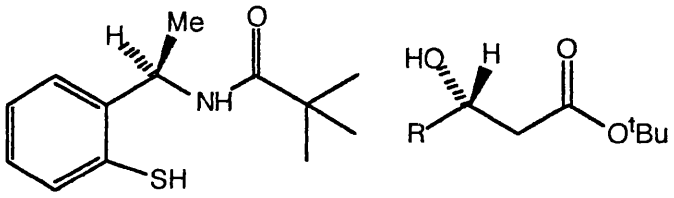


(**IV**)



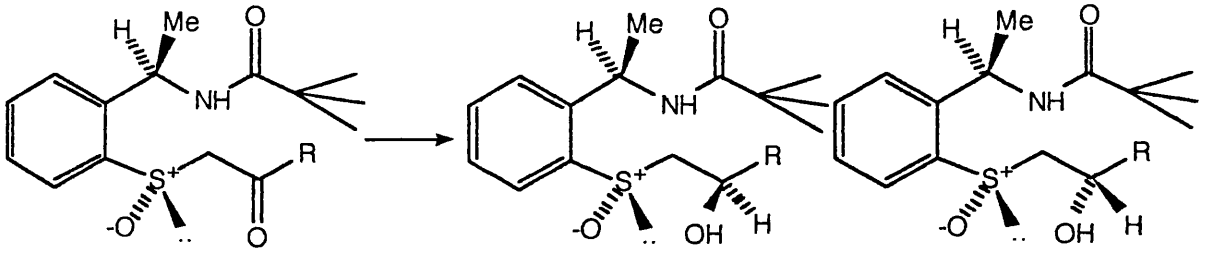
(**V**)

Aluminium amalgam reduction of (V) enabled assignment of the epimeric position in (V) by conversion to β-hydroxyesters (VI) with the sulphur moiety recovered as thiol (VII).



(VII) (VI)

The unprecedented reaction of (I) with ketone enolates resulted in the formation of β-ketosulphoxides (VIII) as single epimers at the sulphur atom, with inversion of configuration as proved by single crystal x-ray determination. β-Ketosulphoxides (VIII) were selectively reduced to the corresponding β-hydroxysulphoxides (IX) with high diastereoselectivity.



(VIII) *trans*-(IX) *cis*-(IX)

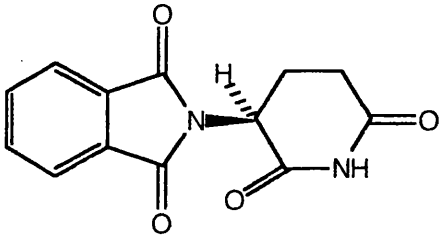
The combination of the reduction of cyclic β-ketosulphoxides (VIII) followed by thermal elimination of the sulphoxide resulted in the formation of cyclic allylic alcohols with high enantiomeric excess. Reduction of the sulphur residues generated thiol (VII).

To complete the regeneration sequence a means for transforming thiol (VII) to sulphinic acid (III) was required. Treating (VII) in refluxing aqueous methanol with sodium periodate and subsequent treatment of the crude reaction mixture with aqueous sodium hydroxide resulted in the formation of (III) in 80% yield.

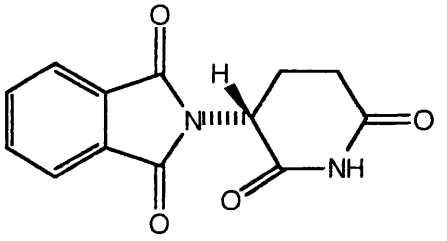
Sulphinamide (I) represents a novel source of homochiral sulphoxide which may be easily regenerated after controlling asymmetric processes with high degrees of selectivity.

1.0 INTRODUCTION.

The synthesis of homochiral compounds is one of the most challenging aspects of modern synthetic organic chemistry.[1] The consequences of ignoring such homochiral compounds were highlighted in the thalidomide (**1**) controversy.[2] Compound (**1**) was originally sold as the racemate, but it was later established that only one enantiomer (the (S)-stereoisomer) had the required anti-emetic activity whilst the other enantiomer was shown to be teratogenic.



(S)-Thalidomide (**1**)



(R)-Thalidomide (**1**)

1.1. The Generation of Homochiral Compounds

There are three distinct methodologies for generating homochiral compounds.

1.1.1 Resolution of racemic compounds.[3]

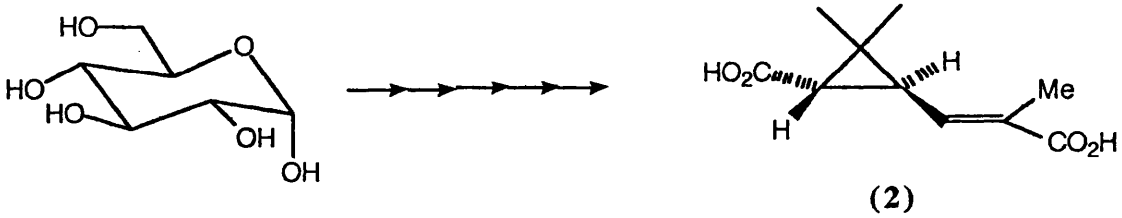
This process relies upon the conversion of the racemic compound into a pair of diastereoisomers by the reaction with an enantiomerically pure substrate. The two diastereoisomers can then be separated using conventional techniques, and with the removal of the chiral resolving handle, the two enantiomers can be released in homochiral form.

A modern approach to this resolution technique has been the utilization of chiral stationary phases in H.P.L.C. In this adaptation of resolution, the racemic mixture is applied to the column and due to the different binding interactions between each enantiomer and the chiral stationary phase, the two enantiomers have different retention times, and hence separation occurs.

Both approaches are based on two simple criteria. The first is that the racemic molecule possesses functionality which can be used to append the resolving agent, or for chiral stationary phase H.P.L.C., functionality for binding to the stationary phase. The second criteria is that once the chiral resolving handle has been attached or bound, there are sufficient physical differences between the formed diastereoisomers to enable easy separation.

1.1.2 Use of the "Chiral pool".

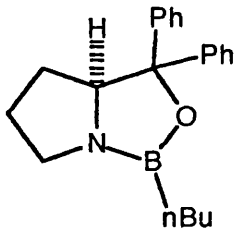
Nature provides the synthetic chemist with a wide range of homochiral compounds which can be used as basic building blocks. These building blocks are usually in the form of carbohydrates and amino acids and much work has been carried out developing methods for converting such compounds into homochiral target molecules. An example of this approach is the synthesis of the insecticide (+)-chrysanthemic acid (**2**)[4] from D-glucose.



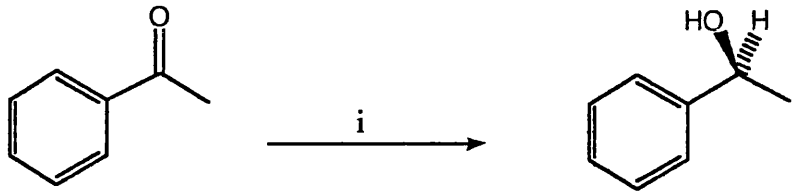
(**2**)

1.1.3 Asymmetric synthesis.

The conversion of a prochiral molecule to a homochiral molecule[5] is synthetically attractive as a method for generating homochiral compounds. There are two main approaches in this area. The first involves the conversion of the prochiral compound *via* the use of an external chiral reagent. An excellent example of such an approach is the oxazoborolidine carbonyl reducing agent (**3**) introduced by Corey[6] (Scheme 1).



(3)

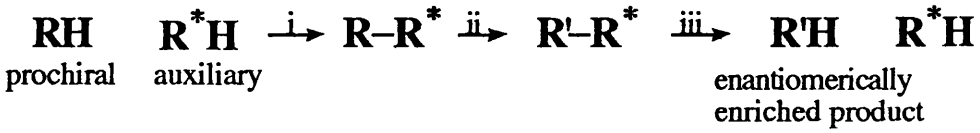


99% e.e

i 0.6 equivalents Borane dimethylsulphide, 10mol% (3), tetrahydrofuran.

Scheme 1

There are a wide variety of such external reagents applicable to a variety of functional group manipulations, e.g. asymmetric epoxidation of allylic alcohols[7] and unactivated double bonds[8], asymmetric hydrogenation[9]and the enzymatic reduction of ketones.[10] The second approach relies on chiral auxiliaries.[11] In this approach a homochiral molecule is appended to the prochiral molecule. The asymmetric transformation is controlled by the appended auxiliary to give an excess of one diastereoisomer. The chiral auxiliary is then removed to give the enantiomerically enriched compound (Scheme 2).



i Coupling of chiral auxiliary, ii Asymmetric transformation controlled by the auxiliary, iii Removal of the auxiliary.

Scheme 2

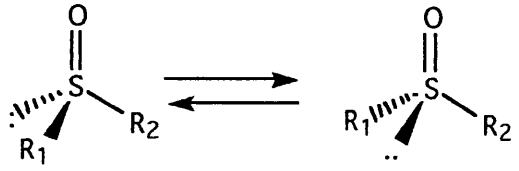
The drawback of utilizing such an approach is that the prochiral substrate must contain functionality through which the chiral auxiliary can be appended.

1.2 The Chiral Sulphoxide Moiety as a Chiral Controller.

1.2.1 Physical characteristics of a chiral sulphoxide.

The sulphoxide is the tri-coordinated form of an oxidised sulphur containing compound, occupying distorted pyramidal geometry. The nature of the sulphur-oxygen bond is uncertain with the bond lengths observed in crystal structures suggesting a double bond whereas the infra-red data suggest a bond order of approximately 1.5.[12] The sulphoxide would be electrophilic at sulphur, hence the chemistry should be dominated by nucleophilic displacement.

The chiral sulphoxide group is peculiarly characterized by the presence of at least three stereoelectronically different ligands, the lone pair, the oxygen atom and two alkyl or aryl substituents. The rate of pyramidal inversion[13] for a series of unsymmetrically substituted sulphoxides has been determined; this thermal stereomutation occurs at a reasonable rate only at temperatures above 200°C, unless a benzylic sulphoxide is present. In such a system stereomutation occurs *via* a different reaction pathway at a lower temperature, typically 130-150°C.



$\Delta H^{\dagger}$ = 146-176 kJ mol^{-1}
$\Delta S^{\dagger}$ = -8 to +4 e.u.

e.g., R_1=Me, R_2=p-Tol

$\Delta H^{\dagger}$ = 37.4 $kJmol^{-1}$, $\Delta S^{\dagger}$ = -8 e.u., k (220°C) = 0.49 x 10^5 s^{-1}

Thus, the sulphoxide unit will retain its configuration under the temperature range encountered under normal reaction conditions.[14]

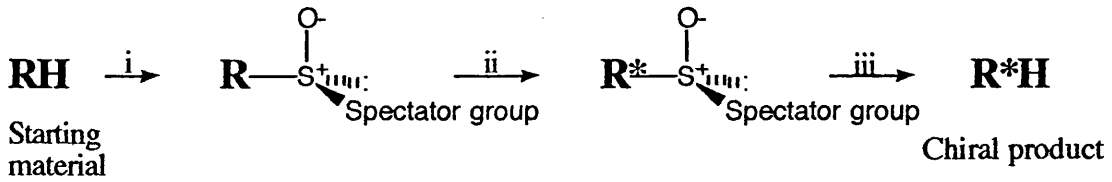
1.2.2 Stereocontrol by the chiral sulphoxide.

The standard sulphoxide stereocontrolling ligand carries a spectator group. The spectator group's role is simple; it must control the regiochemistry involved in the

reductive removal of the sulphoxide, i.e. it must have a greater affinity for sulphur than the asymmetrically transformed compound. The most common spectator group is a substituted aromatic ring e.g. 4-tolyl.

The sulphoxide moiety has been shown to be a highly effective controller[15] in a wide range of asymmetric processes.

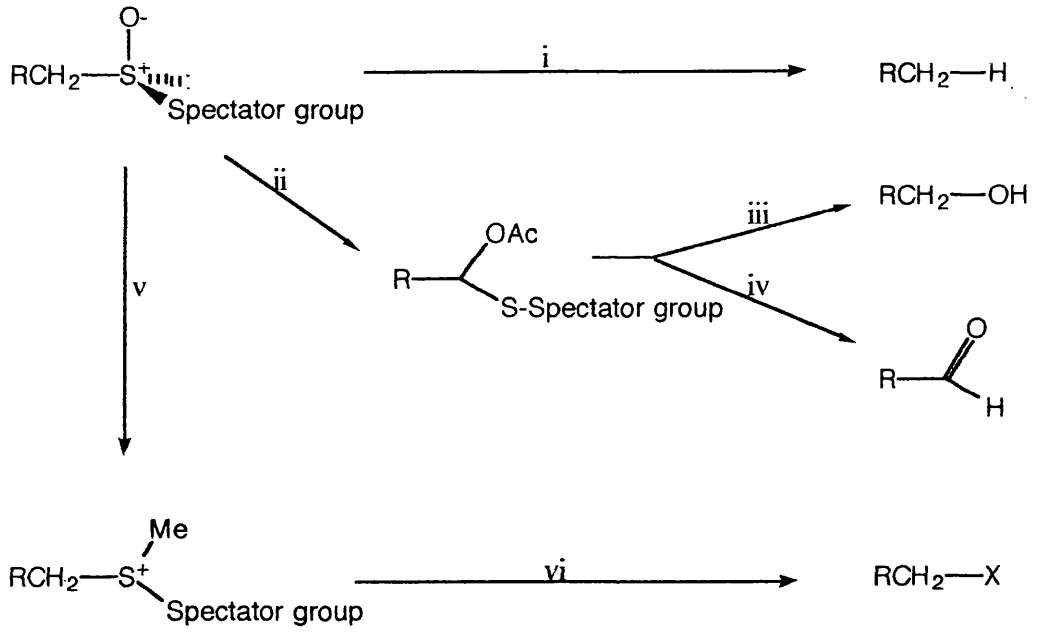
The first stage in any such pathway, the introduction of the chiral sulphoxide will be discussed in the next section. The second step in the process, the sterocontrolled reaction, will be discussed shortly. The final synthetic process in the sequence is the removal of the sulphoxide (Scheme 3).



i Introduction of sulphoxide, ii Asymmetric transformation, iii Removal of sulphoxide.

Scheme 3

The sulphoxide can be removed by a variety of methods to generate an array of functional groups (Scheme 4). The sulphoxide can be reductively removed (i in scheme 4 *via* Raney™ Nickel[16] or aluminium amalgam[17]) to leave the unfunctionalized hydrocarbon. The sulphoxide can be subjected to acetic anhydride/sodium acetate (ii in scheme 4[18] -Pummerer reaction) to generate a 1,1-acetoxysulphide, which upon treatment with base (iv in scheme 4) liberates an aldehyde or ketone. Treatment of the same 1,1-acetoxysulphide with lithium aluminum hydride[19] generates the alcohol (iii in scheme 4). Deoxygenation[20] of the sulphoxide followed by S-methylation[21] would generate the sulphonium salt (v in scheme 4). These sulphonium salts can then be treated with a nucleophile (either in an *intra-* or *inter-* molecular sense) to furnish synthetically useful compounds[22] (vi in scheme 4).



i Raney™ Nickel or aluminium amalgam, ii Acetic anhydride, sodium acetate, iii Lithium aluminium hydride, iv Aqueous base, v Triphenylphosphonium iodide followed by trimethyloxonium tetrafluoroborate, vi Nucleophile X

Scheme 4

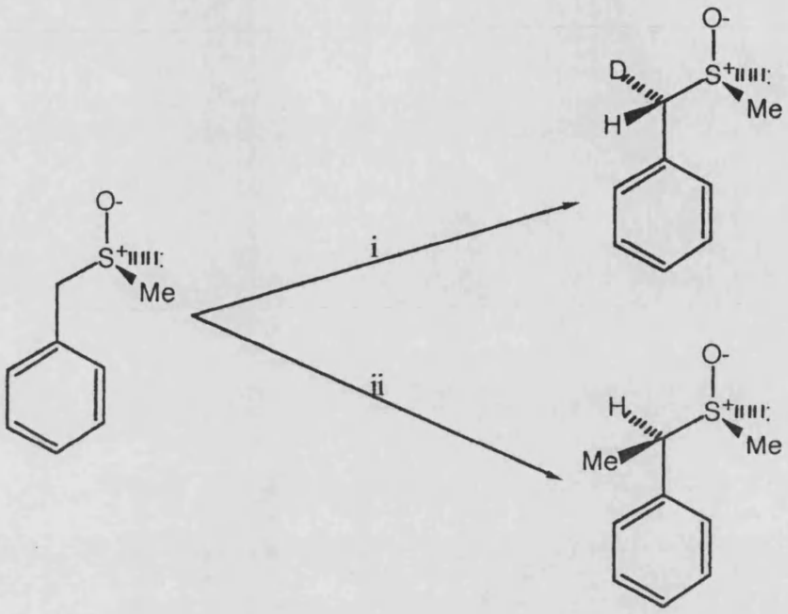
The stereocontrolling chemistry can be divided into two distinct categories;[23]

i) Control at the α-carbon,

ii) Control at the β-carbon.

1.2.3 Control at the α-position.

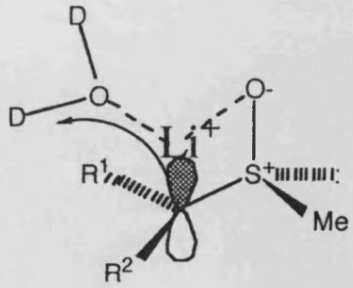
The chemistry at the α-carbon[24] is derived from the acidity of the *alpha* protons (pK_a 33)[25] due to stabilization of the anion formed, by the electronegative sulphoxide. Subsequent alkylations of the anion can be performed with a high degree of stereoselectivity. Durst[26] has achieved highly diastereoselective *syn*-methylation and *anti*-deuteration of benzyl sulphoxides (Scheme 5)



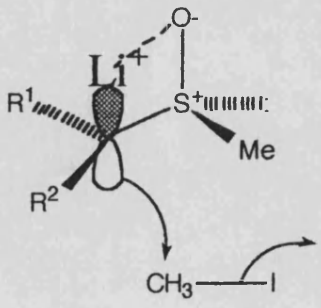
i Methyl lithium, tetrahydrofuran; followed by D_2O, ii Methyl lithium, tetrahydrofuran; followed by methyl iodide.

Scheme 5

Studies[27] have shown that the *syn-anti* stereoselectivity is due to the nature of the reacting electrophile. Electrophiles having the ability to coordinate to the metal counter ion proceed to give the "retention" product, i.e. from the same side as the anion, whilst electrophiles without the ability to coordinate give products resulting from "inversion" (Scheme 6).



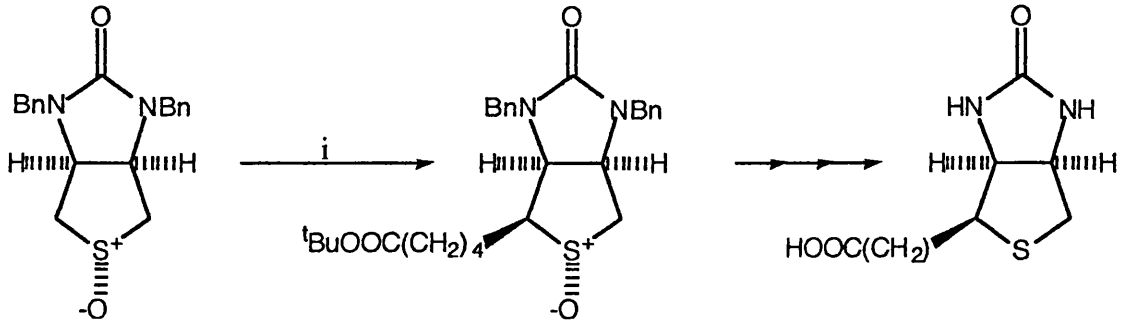
anti-deuteration *via* coordination of incoming electrophile



syn-methylation

Scheme 6

This approach was first applied to total synthesis by Marquet[28] in the preparation of *dl*-biotin (**4**). Deprotonation of the *meso*-sulphoxide with methyllithium and quenching with the iodoelectrophile gave the product (**5**) with total diastereoselective control (Scheme 7). Compound (**5**) was further elaborated to give required (**4**).

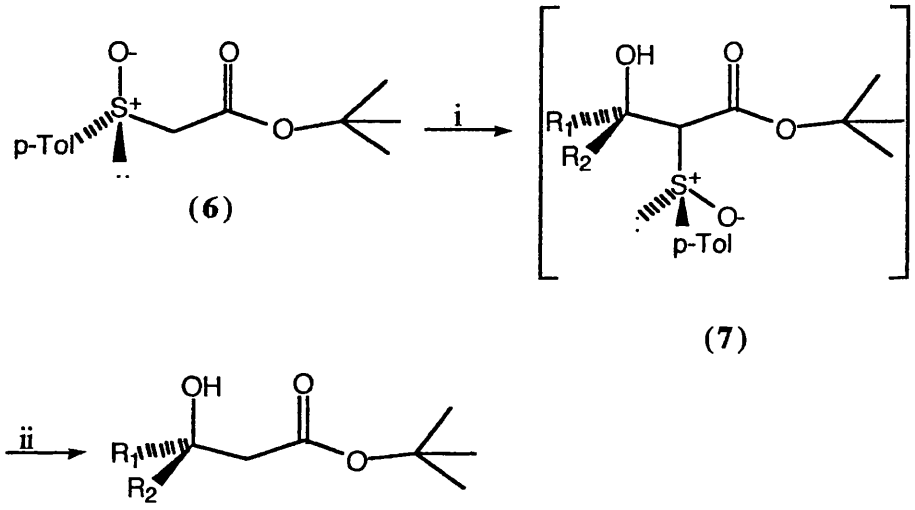


(**5**) (**4**)

i Methyllithium, diglyme, HMPA; followed by I(CH$_2$)$_4$COO^{t}Bu.

Scheme 7

Deprotonation of sulphinylacetate (**6**) with *tert*-butylmagnesium bromide followed by treatment of the anion with a series of carbonyl compounds resulted in the formation of unstable aldol adducts (**7**).[29] These adducts when treated with aluminium amalgam generated β-hydroxy esters in good enantiomeric excess (Scheme 8 and table 1).



(**6**) (**7**)

i *tert*-Butylmagnesium bromide, followed by $R_1R_2C{=}O$, ii Aluminium amalgam, 10% aq. tetrahydrofuran..

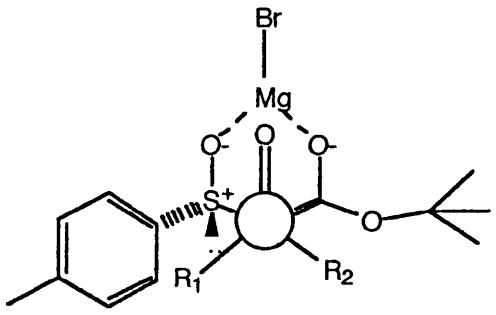
Scheme 8

R_1	R_2	%e.e of alcohol	Yield %
H	Ph	91	85
Me	Ph	68	75
Ph	CF_3	20	75
H	n-heptyl	86	80
Me	Cyhexyl	95	95
Me	$(CH_2)_2OAc$	40	90

Synthesis of β-hydroxyesters from (6) and carbonyls followed by aluminium amalgam reduction.

Table 1

The highly chelated transition state (**8**) has been proposed (figure 1) to explain the high stereocontrol observed. Delivery of the carbonyl compound to the less hindered face of the enolate results in extremely high α-control. The R groups on the carbonyl compound then adopt the most favourable orientation to give good stereocontrol.



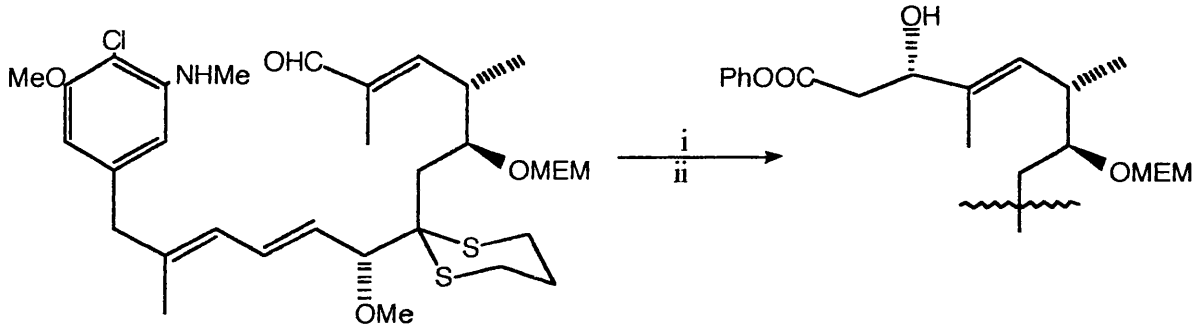
(8)

The transition state proposed to rationalize the observed high selectivity.

Figure 1

This approach has been applied to the synthesis of the anti-tumour agent Maytansin (**9**). Condensation of the sulphinyl acetate (**6**) with the aldehyde (**10**), followed by

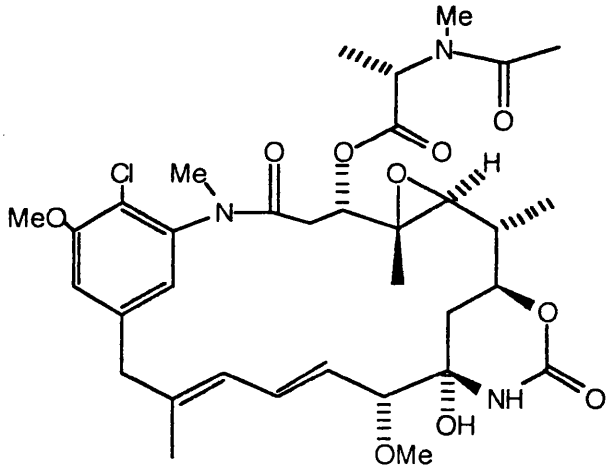
desulphurization gave the required β-hydroxyester (**11**) in 86% diastereoisomeric excess (Scheme 9) and (**11**) was further elaborated to give (**9**).[30]



(**10**) (**11**)

i t-Butylmagnesium bromide, (**6**), ii Aluminium amalgam, 10% aq. tetrahydrofuran.

Scheme 9



Maytansin (**9**)

1.2.4 Control at the β-position.

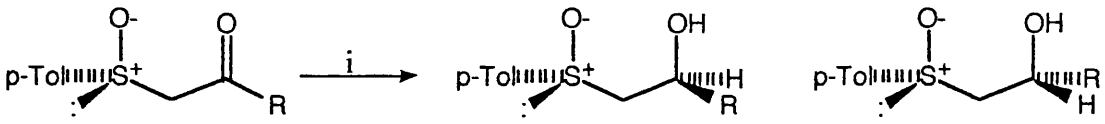
The β-control falls into two major categories;

a) Reactions of β-ketosulphoxides,

b) Reactions of vinylsulphoxides.

1.2.5 Reactions of β-ketosulphoxides.

Treatment of β-ketosulphoxides with reducing agents resulted in the formation of β-hydroxysulphoxides of varying diastereoselectivity, the observed selectivity dependent on the reducing agent used. The methodology[31] has been developed to the point that from a single β-ketosulphoxide (**12**) either diastereoisomer of the β-hydroxysulphoxide (**13**) can be prepared with very high stereocontrol[32] (table 2 and Scheme 10).



(**12**) *trans*-(**13**) *cis*-(**13**)

i Reducing agent (see table 2).

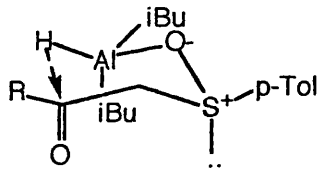
Scheme 10

Treatment of the β-ketosulphoxide with diisobutylaluminum hydride (DIBAL-H) resulted in formation of the *trans*-hydroxysulphoxide. The proposed conformation illustrated in figure 2[33] has been used to explain the high selectivity observed. In the proposed model DIBAL-H is thought to complex with the oxygen of the sulphoxide to generate the aluminate. Hydride transfer then occurs in an intramolecular sense *via* the sterically less demanding chair-type transition state.

R	Reducing agent	*Cis:trans*	Yield%
Ph	DIBAL-H	>5:95	95
"	DIBAL-H $ZnCl_2$	>95:5	90
$Ph(CH_2)_2$	DIBAL-H	7:93	95
"	DIBAL-H $ZnCl_2$	>95:5	95
$n\text{-}C_8H_{17}$	DIBAL-H	5:95	95
"	DIBAL-H $ZnCl_2$	>95:5	92
$n\text{-}C_{13}H_{27}$	DIBAL-H	5:95	95
"	DIBAL-H $ZnCl_2$	> 95:5	95

Reduction of (12) with DIBAL-H and DIBAL-H zinc (II) chloride.

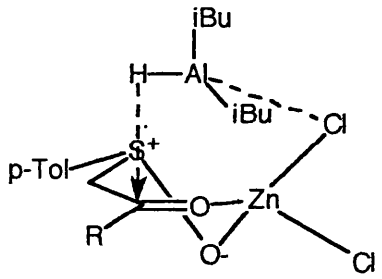
Table 2



Proposed conformation for the DIBAL-H reduction of β-ketosulphoxides

Figure 2

Higher selectivities for the *cis*-hydroxysulphoxides have been achieved by utilizing zinc dihalide Lewis acids as chelation agents, in conjunction with the DIBAL-H. The zinc dihalides coordinate to the oxygens of the sulphoxide and the carbonyl to form a rigid chelated species as shown in figure 3. The DIBAL-H is then directed by complexation to the geometrically well situated pseudo-axial halide leading to a bimetallic bridged species.[34]

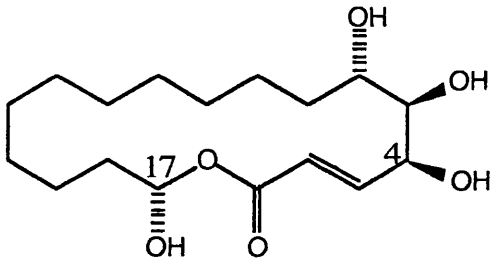


Proposed conformation for the DIBAL-H zinc (II) chloride reduction of β-ketosulphoxides.

Figure 3

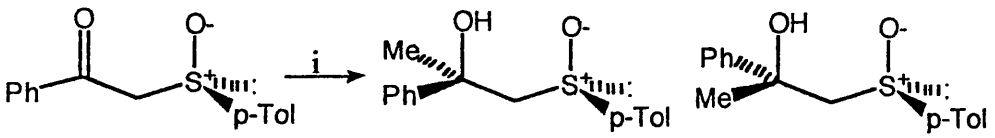
In this proposed model the hydride transfer occurs again in an intramolecular fashion to the top face of the carbonyl leading to high *cis*-selectivity (figure 3).

This methodology has been applied to the synthesis of a wide range of poly-hydroxylated natural products. An example of such a synthesis is the macrolide aspicilin (**14**).[35] Both reduction protocols were utilized in the synthesis to generate the required hydroxyl stereochemistry at C-4 and C-17.



(14)

Limited success has been achieved in introducing nucleophiles other than hydride. Attempts by Fujisawa[36] and co-workers to introduce a methyl nucleophile met with unsatisfactory success (Scheme 11). Reaction of β-ketosulphoxide (**15**) with a series of mild methyl nucleophiles resulted in the formation of the tertiary alcohols (**16**) (table 3).



(15) *trans*-**(16)** *cis*-**(16)**

i Methyl nucleophile (see table), -20°C.

Scheme 11

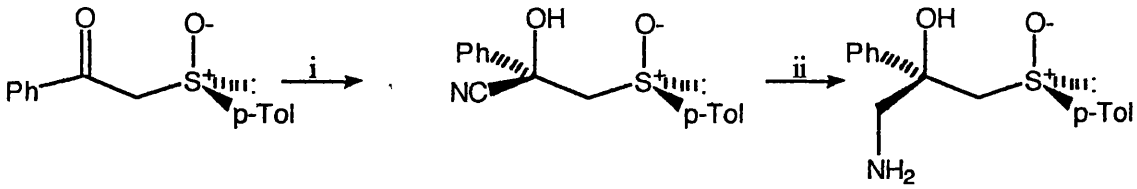
Me-Metal	*trans*:*cis*	Yield
$MeTiCl_3$	82:18	79%
$MeMgBr\text{-}CeCl_3$	16:84	30%
Me_3Al	26:74	66%

Addition of methyl nucleophiles to (15).

Table 3

Deprotonation of the acidic methylene, flanked by both the sulphinyl and the ketone, provided the competing pathway to nucleophilic attack.

The introduction of cyanide, *via* diethylaluminium cyanide, into the β-ketosulphoxides has been achieved by Garcia-Ruano and co-workers[37] with very high diastereoselectivity to generate cyanohydrin (**17**) (greater than 96% diastereomeric excess) which upon reduction furnished ethanolamines (**18**) in high stereochemical yields (Scheme 12).



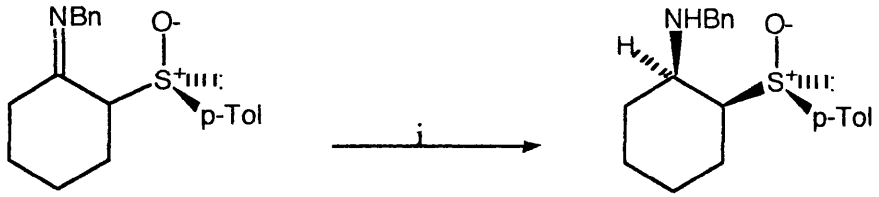
(15) **(17)** **(18)**

i Diethylaluminium cyanide, ii Lithium aluminium hydride.

Scheme 12

The related reduction of cyclic β-iminosulphoxides[38] with hydride sources has been investigated by Garcia-Ruano and co-workers[39] (Scheme 13). The initial results

appeared promising with the reduction of (**19**) with DIBAL-H generating aminosulphoxides (**20**) with high diastereoisomeric (up to 100%) and enantiomeric control (upto 95%).



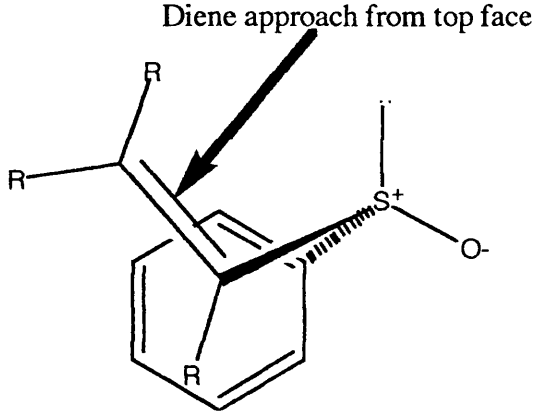
(**19**) (**20**)

i DIBAL-H, tetrahydrofuran, -78°C.

Scheme 13

1.2.6 Reactions of vinylsulphoxides

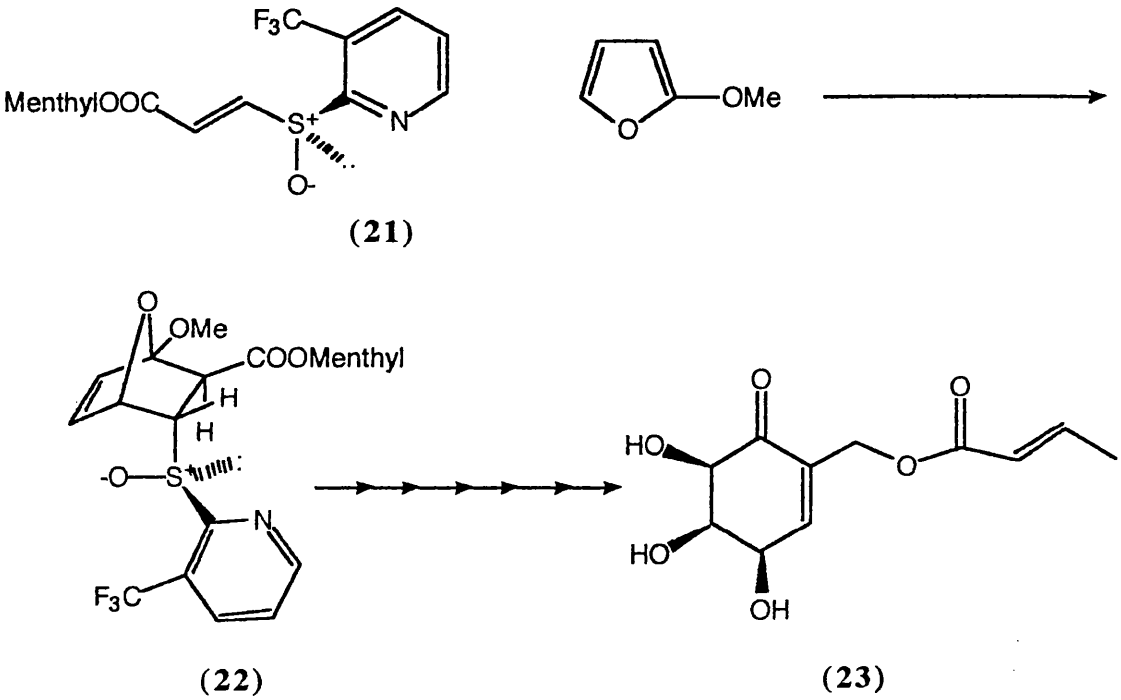
The two processes which come under this heading are the Diels-Alder[40] reaction and the Michael 1,4-conjugate addition[41] with both areas extensively studied. In the Diels-Alder chemistry the sulphinyl unit appears on the dienophile, giving facial selectivity towards the incoming diene (figure 4).



Conformation of vinyl sulphoxide during Diels-Alder cyclisation.

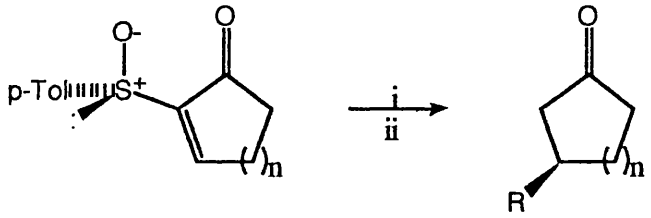
Figure 4

Highly diastereoselective reactions have been achieved utilizing this approach. Reaction of the chiral dienophile[42] (**21**) with 2-methoxyfuran resulted in the formation of the adduct (**22**) as a single stereoisomer which was elaborated by Koizumi and co-workers to give the required glyoxalase I inhibitor[43] (**23**) (Scheme 14).



Scheme 14

Posner[41] has recently reviewed the Michael additions to sulphinylcycloalkenones. Again high stereocontrol is observed in the reactions due to the arylsulphinyl moiety effectively blocking one of the stereogenic faces of the double bond (Scheme 15 and table 4).



i R-Metal (see table), tetrahydrofuran, ii Aluminium amalgam.

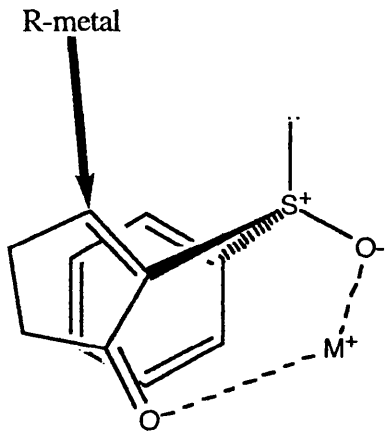
Scheme 15

A similar transition state to that proposed for the Diels Alder chemistry is suggested for this highly stereospecific process based upon the metal cation acting as a chelation agent (figure 5).

R-Metal	R	e.e%	Yield %
MeMgCl	Me	>98	91
$ZnBr_2$/ EtMgBr	Et	80	84
$EtTi(OPr)_3$	Et	>98	67
$ZnBr_2$/ t-BuMgBr	tBu	86	98
$ZnBr_2$/ AllylMgBr	Allyl	98.7	75
$ZnBr_2$/ PhMgBr	Ph	92	70

Michael addition of nucleophiles to sulphinylcycloalkenones.

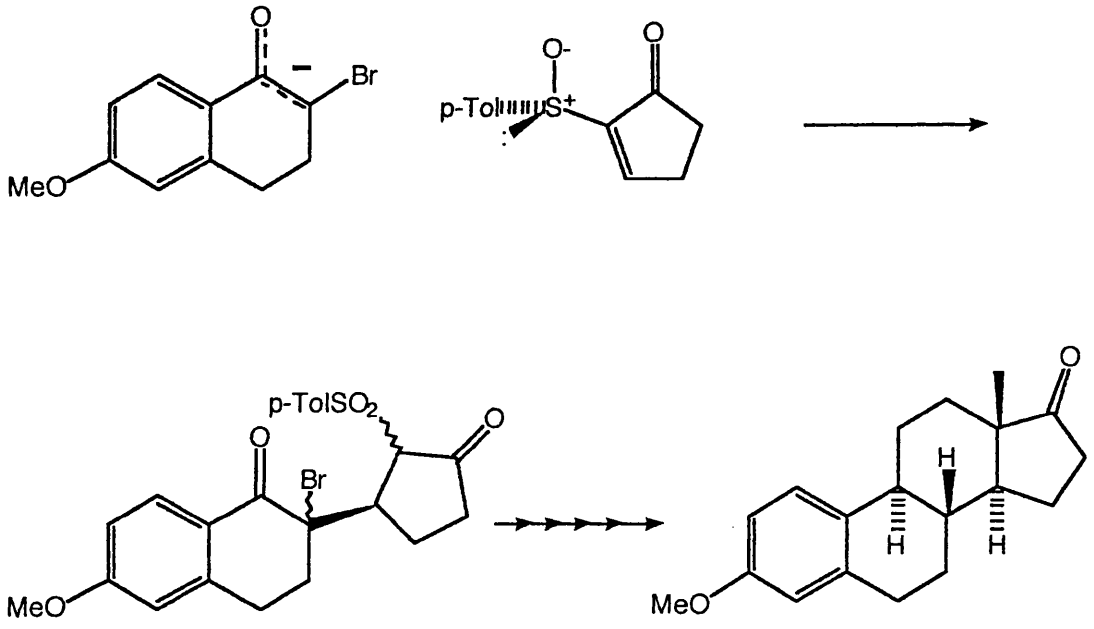
Table 4



Conformation proposed to rationalize highly selective addition to sulphinylcycloalkenones.

Figure 5

Posner and co-workers have utilized the methodology in the synthesis of natural (-)-estrone[44] (**24**) (Scheme 16).



(24)

Scheme16.

1.3. Synthesis of Homochiral Functionalised Sulphoxides

There are two major methods for the synthesis of functionalised homochiral sulphoxides;[45]

i Nucleophilic displacement at an existing sulphur chiral centre with net inversion of configuration at sulphur,

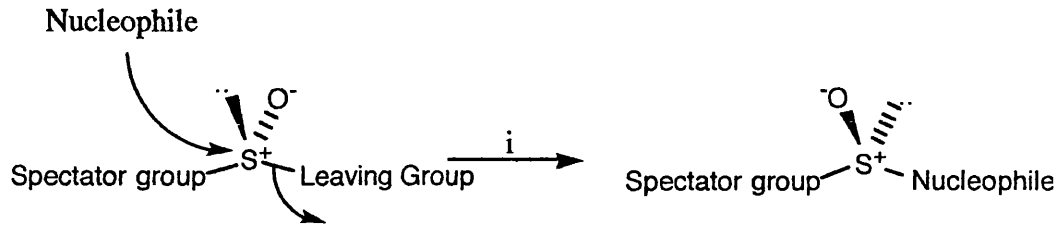
ii The asymmetric oxidation of a prochiral sulphide either by chemical means or *via* biological oxidation,

1.3.1 The Nucleophilic Displacement at an existing sulphur chiral centre.

This methodology requires the synthesis of a variety of homochiral sulphoxide sources, i.e. optically pure compounds which upon reaction with a nucleophile at an existing sulphur chiral centre will generate the required sulphoxide. Such sources fall into two categories;

a) Compounds where the spectator group (the group not undergoing the subsequent asymmetric transformation) is already incorporated. The source also has a

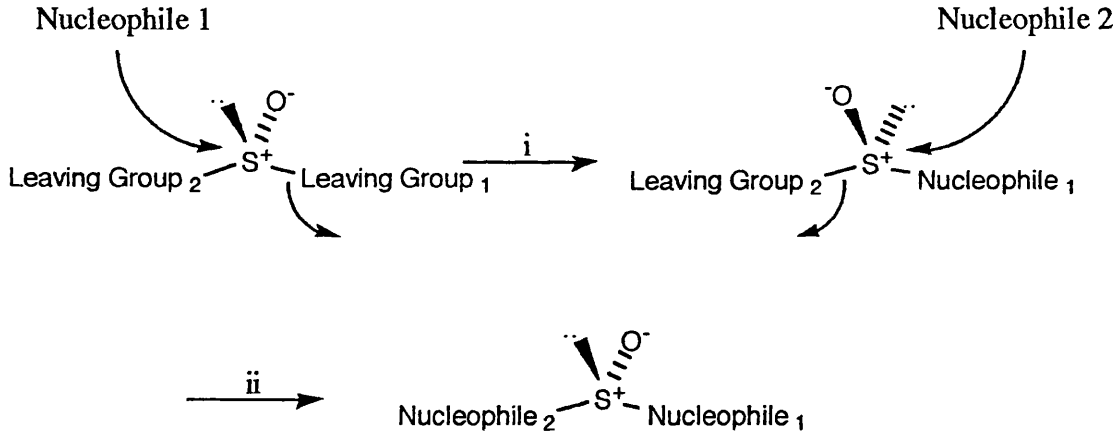
ready leaving group which upon nucleophilic replacement generates the required functionalised sulphoxide (Scheme 17).



i Nucleophile.

Scheme 17

b) The second classification requires the incipient sulphoxide flanked by two leaving groups. Two regiocontrolled sequential nucleophilic displacements are then required to generate the functionalised sulphoxide (Scheme 18).

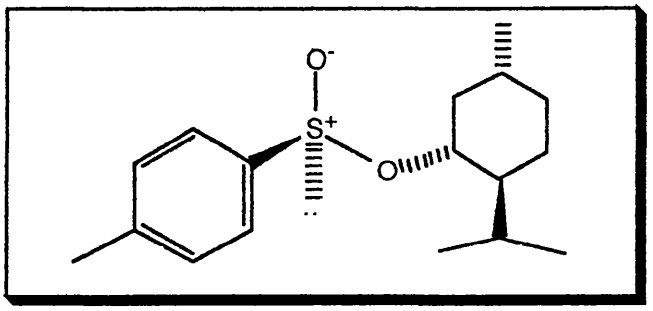


i Nucleophile 1, ii Nucleophile 2.

Scheme 18

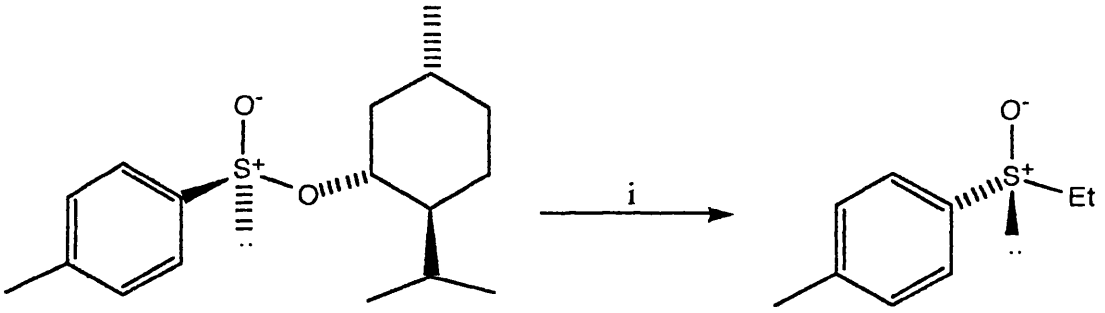
1.3.2 Sources already incorporating the spectator group.

The methodology described within this section revolves around the usage of homochiral sulphinate esters and sulphinamides. The most utilized sulphinate ester to date is (1R, 2S,5R)-(-)-menthyl-(S)-p-tolylsulphinate (**25**).[46]



(1R, 2S,5R)-(-)-menthyl-(S)-p-tolylsulphinate (**25**)

Sulphinate ester (**25**) was first resolved in 1925 by Philips[47] and nucleophilic reactions with this ester were proposed as early as 1926 by Gilman.[48] The first recorded usage of sulphinate ester (**25**) was in 1962 by Andersen[49] who reported the reaction between the Grignard reagent derived from bromoethane and (**25**) (Scheme 19).

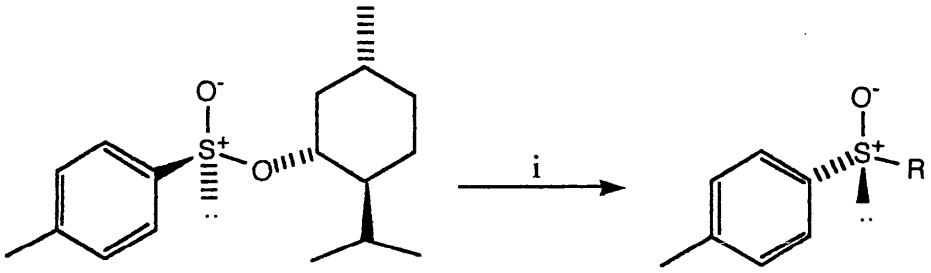


(**25**)

i Ethylmagnesium bromide, diethyl ether, -78°C.

Scheme 19

Work by Mislow[50] and co-workers and Sommer[51] and co-workers have shown unambiguously that the nucleophilic attack of organometallic reagents upon homochiral menthyl sulphinates leads *via* complete inversion of stereochemistry at sulphur to enantiomerically pure sulphoxides. The generality of such nucleophilic displacement chemistry is outlined in table 5 (Scheme 20).



(25)

i See table 5

Scheme 20

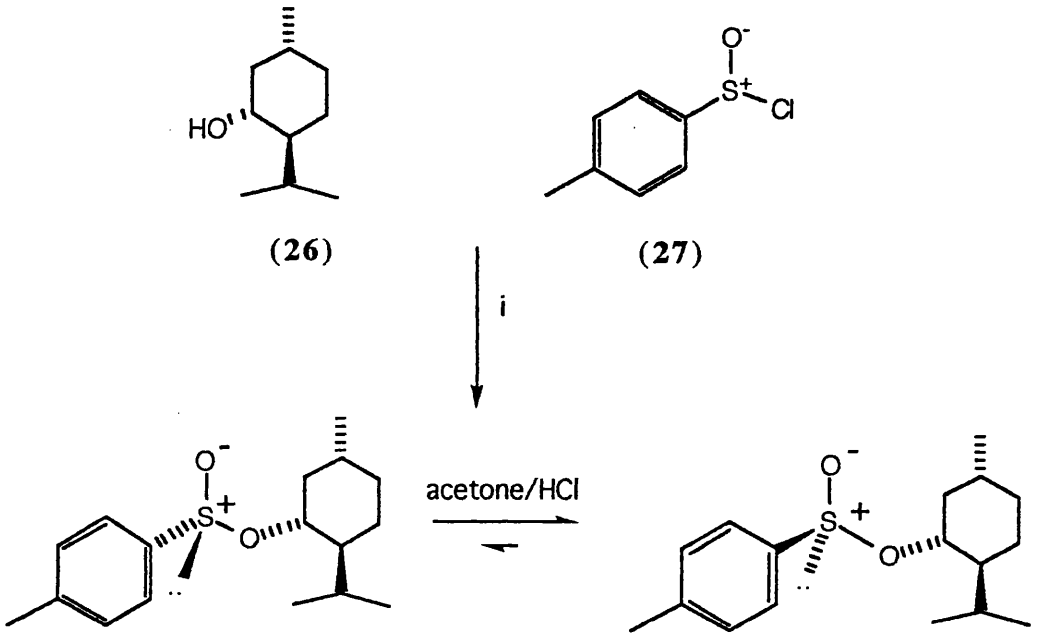
R	Metal	Yield %
Methyl	MgBr	90
Ethyl	MgBr	90
t-Butyl acetate	MgBr	90
Dimethyl methanephosphonate	Li	72
(E)-1-Octenyl	MgBr	60
2-Cyclohexanone	MgBr	70
Phenylmethyl imine	Li	75

Nucleophilic reactions of sulphinate ester (25).

Table 5

In the case of (**25**) the spectator group is the aromatic p-tolyl unit. Sulphinate ester (**25**) was synthesized in low diastereomeric excess (a 2-3:1 mixture) from menthol (**26**) and p-tolylsulphinyl chloride (**27**).

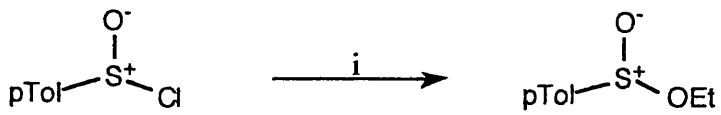
Fortunately[46] the major (S)-(**25**) diastereoisomer crystallized from an acetone solution of the mixture and the minor (R)-epimer may be equilibrated (Scheme 21) under acidic conditions to give reasonable yields of (S)-(**25**).



i Triethylamine, benzene.

Scheme 21

Attempts by Mikozajczyk and Drabowicz[52] to generate a series of enantiomerically enriched sulphinate esters, not containing menthol, by treating p-tolylsulphinyl chloride **(26)** with alcohols in the presence of chiral amines met with limited success. Enantiomeric excesses of up to 45% have been achieved utilizing N,N-dimethylmenthylamine in this methodology (Scheme 22).

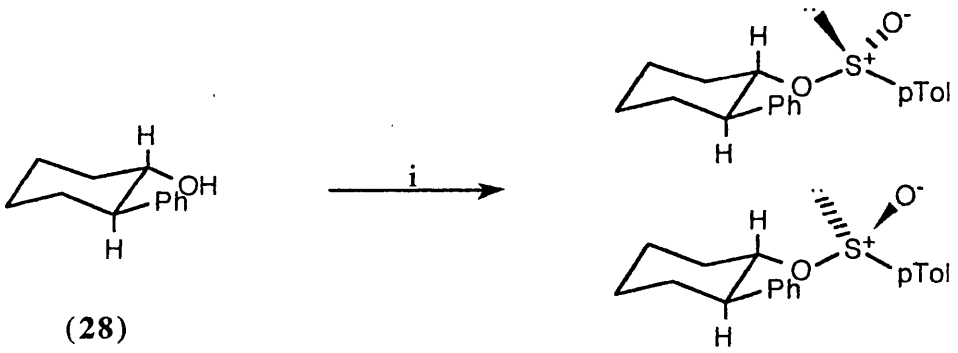


i N,N-dimethylmenthylamine, ethanol.

Scheme 22

Whitesell[53] and co-workers have used the enantiomerically pure *trans*-2-phenylcyclohexanol **(28)** auxiliary in generating a series of homochiral sulphinate

esters. The reaction between (**28**) and (**27**) showed a higher kinetic selectivity (4:1) than achieved in the comparable reaction with menthol (**26**). The diastereoisomeric adducts were readily separable by column chromatography and isolated as stable crystalline solids (Scheme 23).



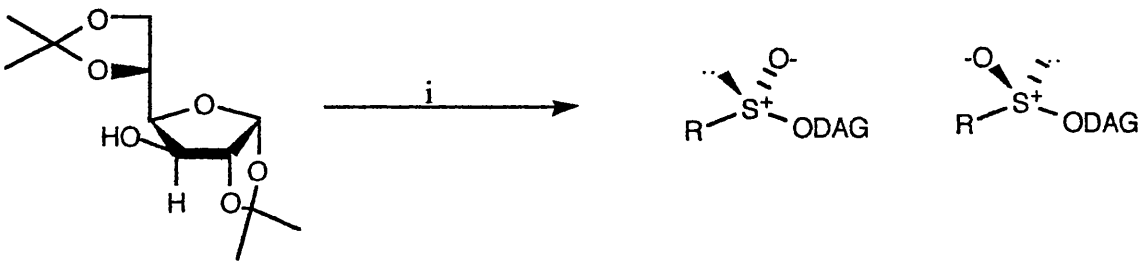
(**28**) (**29**)

i (**27**), pyridine, ether, -78°C.

Scheme 23

Reaction of the diastereoisomerically pure sulphinate esters (**29**) with organometallic reagents resulted in the formation of homochiral functionalized sulphoxides with clean inversion of stereochemistry at sulphur.

All the previously described approaches have been shown to be ineffectual in preparing homochiral crystalline sulphinate esters where the spectator group is methyl. Andersen[54] and co-workers in 1984 described the synthesis of a crystalline methylsulphinate ester by replacing (**26**) with cholesterol. However, a superior approach has been described by Llera[55] and co-workers in which (**26**) has been substituted with diacetone-D-glucose (DAG) (**30**). By varying the tertiary amine base used in the condensation between methylsulphinyl chloride (**31**) and (**30**) either epimer of the methyl-DAG sulphinate (**32**) may be formed with high diastereomeric excesses (Scheme 24). This approach has been successfully extended to a wide variety of sulphinyl chlorides (table 6). The subsequent reaction of (**32**) with nucleophiles resulted in the formation of functionalised methyl sulphoxides with inversion of configuration at sulphur.



(**30**) (R)-(**32**) (S)-(**32**)

i RSOCl, base, solvent, -78°C.

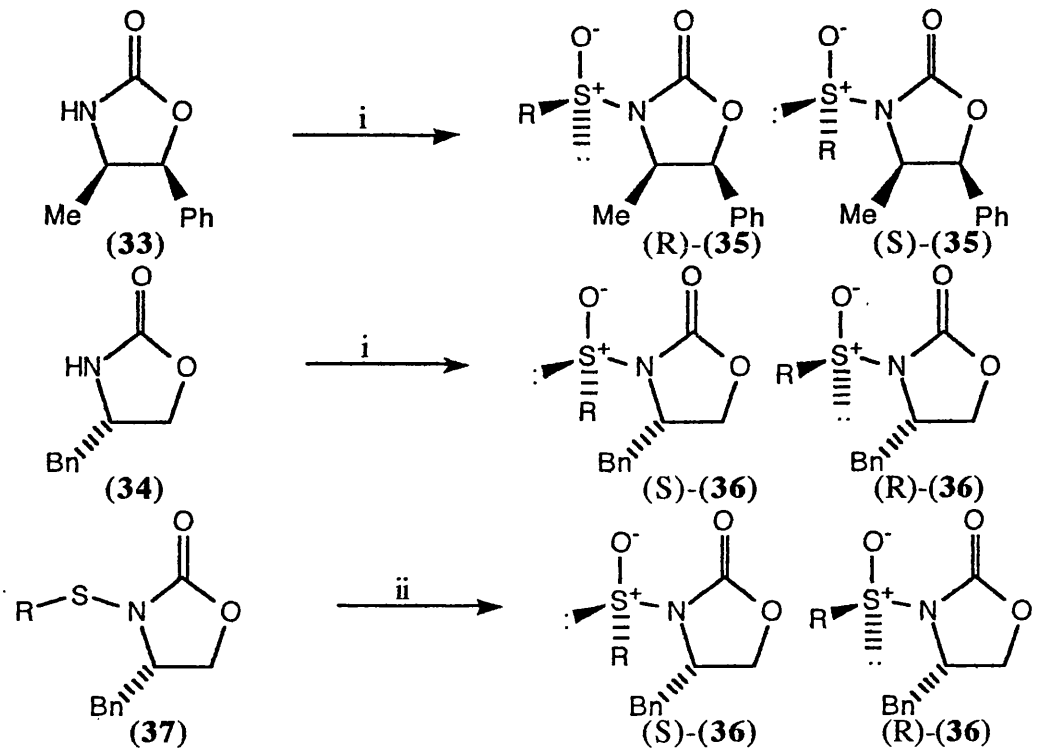
Scheme 24

R	Base	Solvent	R/S	Yield %
Me (**31**)	Pyridine	tetrahydrofuran	93/7	87
Me (**31**)	i-Pr2NEt	toluene	>2/98	90
Et	Pyridine	tetrahydrofuran	86/14	85
Et	i-Pr2NEt	toluene	>2/98	90
n-Pr	Pyridine	tetrahydrofuran	85/15	75
n-Pr	i-Pr2NEt	toluene	4/96	80
Tol	Pyridine	tetrahydrofuran	86/14	84
Tol	i-Pr2NEt	toluene	6/94	87

Reaction of sulphinyl chlorides with (30).

Table 6

In a comparable study Evans[56] and co-workers have used the oxazolidinones derived from (4*R*, 5*S*)-norephedrine (**33**) and (4*S*)-phenylalanine (**34**) as sources of homochiral sulphoxide. Condensation of these oxazolidinones with sulphinyl chlorides proceeds with low diastereoselectivity to give the readily separable N-sulphinyloxazolidinones, (**35**) and (**36**) respectively, in reasonable isolated yields. In concert with this study, the related oxidation of the N-sulphenyloxazolidinones (**37**) with *meta*-chloroperbenzoic acid was investigated, which proceeded to give the opposite diastereoisomer in excess (Scheme 25 and table 7).



i n-Butyl lithium, RSOCl, ii *meta*-Chloroperbenzoic acid.

Scheme 25

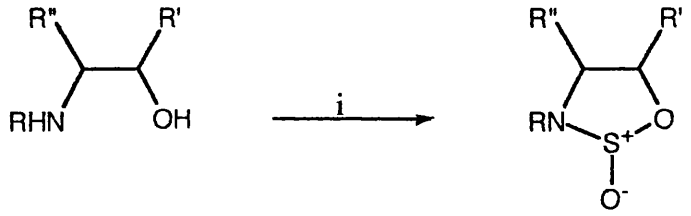
R-S(O)$_n$-Oxazolidinone	S_S:R_S	Yield of major isomer %
pTolSO-(**33**)	34:66	69
PhSO-(**33**)	23:77	61
pTolSO-(**34**)	68:32	61
Ph-SO(**34**)	67:33	50
Ph-S-(**37**)	29:71	68
tBu-S-(**37**)	42:58	49

Synthesis of sources for homochiral sulphoxides based on oxazolidinones.

Table 7

1.3.3 Sources containing two leaving groups.

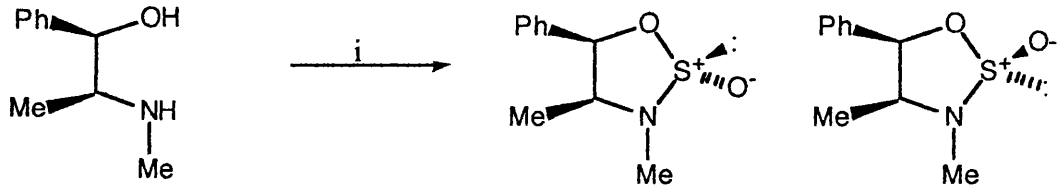
Deyrup[57] and Moyer in 1969, reported that upon reaction of 1,2-ethanolamines with thionyl chloride, aminosulphites were generated instead of the expected aziridines (Scheme 26). However, no diastereoisomeric excesses or any further reactions were reported. These aminosulphites have the potential of acting as sulphoxide sources *via* two sequential nucleophilic displacements.



i Thionyl chloride, triethylamine.

Scheme 26

This potential was exploited when a more detailed investigation into the synthesis of these cyclic aminosulphites was undertaken in 1973 by Wudl and Lee.[58] (4S, 5R)-Ephedrine (**38**) when treated with thionyl chloride gave a 72:28 diastereoisomeric mixture of aminosulphites (**39**) (Scheme 27). The major diastereoisomer was assigned as *trans*-(**39**).

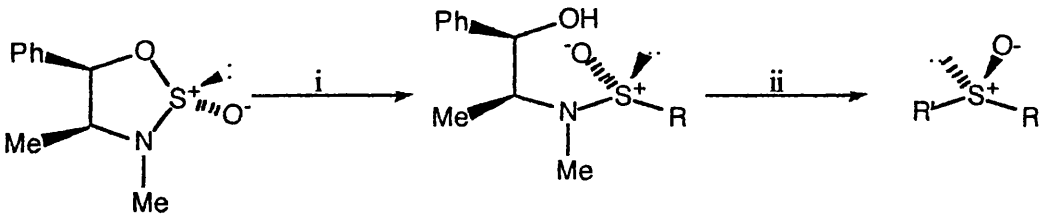


(**38**) *trans*-(**39**) *cis*-(**39**)

i Thionyl chloride, triethylamine, cyclohexane.

Scheme 27

The diastereoisomers were separated and upon treatment of (**39**) with Grignard reagents cleavage of the S-O bond resulted in the formation of sulphinamine (**40**). Further treatment of (**40**) with a second organometallic reagent resulted in the cleavage of the S-N bond to give the required sulphoxide (Scheme 28).



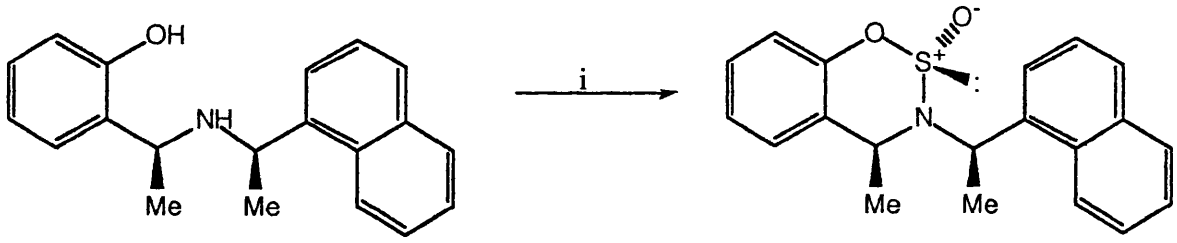
trans-(**39**) (**40**)

i R-MgBr, diethyl ether, ii R'-Metal, tetrahydrofuran.

Scheme 28

This work was modified in 1991 by Snyder and Benson[59] by the utilization of trimethylaluminium, as a Lewis acid, in the addition of the second organometallic and an acid catalyzed epimerisation of the minor *cis*-(**39**) to the major *trans*-(**39**).

In a similar approach Hiroi[60] used (**41**) as a replacement for ephedrine. Reaction of (**41**) with thionyl chloride generated a diastereomeric mixture of aminosulphites which upon treatment with either a protic or Lewis acid resulted in isomerisation to the single diastereoisomer (**42**) (Scheme 29).



(**41**) (**42**)

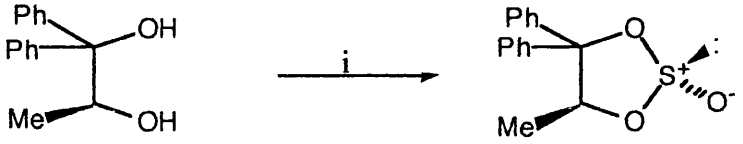
i Thionyl chloride, followed by protic or Lewis acid.

Scheme 29

Treatment of the aminosulphite (**42**) with an organometallic reagent again resulted in S-O bond cleavage, followed by S-N bond cleavage upon treatment with a second organometallic reagent, with inversion of configuration in both steps.

A modification of this approach has been reported by Kagan and co-workers[61] in which the diol (**43**), derived by addition of phenylmagnesium bromide (2 equivalents) to ethyl lactate, was treated with thionyl chloride to give the sulphite (**44**) in an 80%

diastereoisomeric excesses (Scheme 30). Recrystallisation of the diastereoisomeric mixture gave (**44**) as a single diastereoisomer in 70% chemical yield.

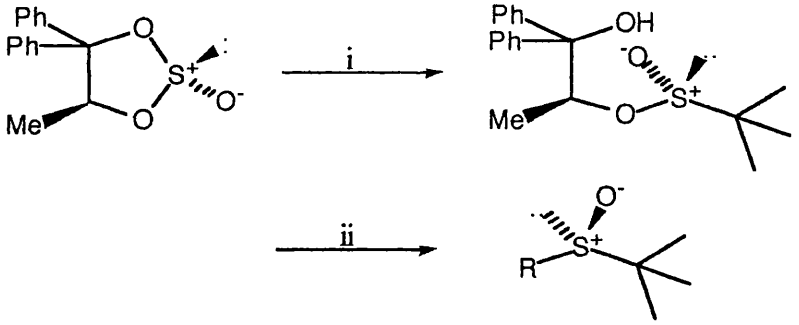


(**43**) (**44**)

i Thionyl chloride, triethylamine, dichloromethane.

Scheme 30

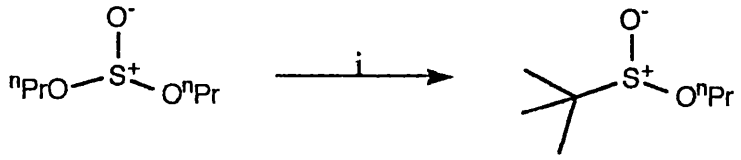
The drawback with this system was a lack of regiocontrol upon treatment of (**44**) with simple organometallic reagents. However, this was rectified by the use of *tert*-butylmagnesium bromide as the initial reagent which proceeded with good (95:5) regioselectivity to afford the sulphinate derived from cleavage at the most hindered site. A second displacement reaction afforded the homochiral *tert*-butylsulphoxide (Scheme 31).[62]



i *tert*-Butylmagnesium bromide, diethyl ether, ii R-metal, tetrahydrofuran.

Scheme 31

In a associated approach Mikozajczyk and Drabowicz[63] took a series of symmetrical sulphites and treated these prochiral sulphites with *tert*-butylmagnesium bromide in the presence of quinine to give sulphinate esters in 74% enantiomeric excess (Scheme 32).



i Quinine , *tert*-butylmagnesium bromide, benzene.

Scheme 32

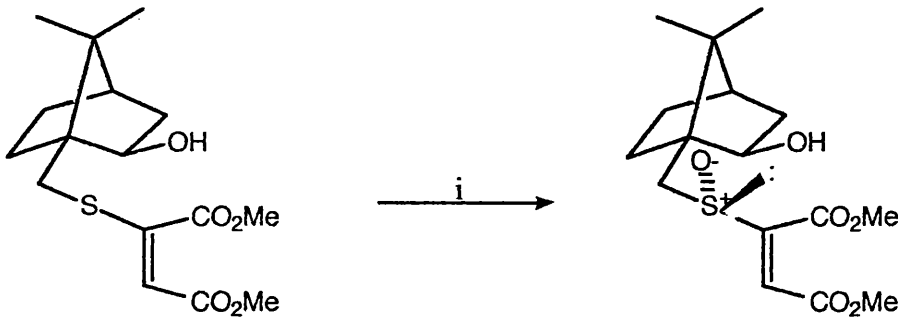
1.3.4 The asymmetric oxidation of a prochiral sulphide either by chemical means or *via* a biological oxidation.[64]

The oxidation of a prochiral sulphide by chemical means can be divided into two distinct categories:

a) the use of an existing chiral centre within the molecule to direct the oxidation,

b) the use of a chiral oxidation system.

The use of camphor[65] based systems as unsymmetrical sulphides allowed for the free hydroxyl group to act as a directing agent for the oxidation of the sulphoxide . The use of dimethyl-(d-isoborneol-10-sulphinyl)maleate (**45**) by Koizumi[66] as a chiral dienophile was effective due to the ease of the selective oxidation (*meta*-chloroperbenzoic acid as oxidant) of the sulphide (**46**) to the corresponding homochiral sulphoxide (Scheme 33).

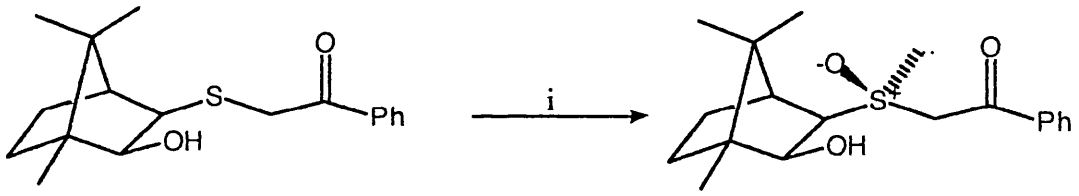


(46) **(45)**

i *meta*-Chloroperbenzoic acid, dichloromethane.

Scheme 33

In a similar approach Yang and workers[67] have used the β-keto-sulphoxide (**47**) in stereochemically defined reductions to give the corresponding β-hydroxysulphoxides. The β-keto-sulphoxide (**47**) was generated *via* the stereospecific oxidation of the sulphide (**48**) (Scheme 34). Again oxidation was directed by the hydroxyl to give the required single epimer.

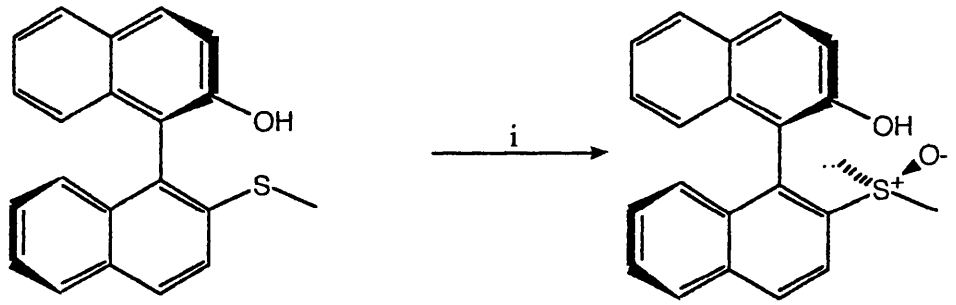


(48) **(47)**

i *meta*-Chloroperbenzoic acid, dichloromethane.

Scheme 34

A similar directed oxidation has been utilized by De Lucchi[68] in the synthesis of the binapthylmethylsulphoxide (**49**). Oxidation of the sulphide (**50**) with *meta*-chloroperbenzoic acid afforded the sulphoxide as a single diastereoisomer (Scheme 35).



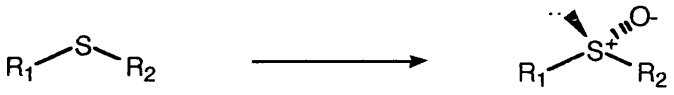
(50) **(49)**

i) *meta*-Chloroperbenzoic acid, dichloromethane.

Scheme 35

The big breakthrough in the asymmetric oxidation of sulphides was described independently by Kagan and workers[69] and Modena[70] and workers, who both utilized a modified Sharpless[7] asymmetric epoxidation procedure. Both methods utilized *tert*-butyl hydroperoxide as the oxidant with the methods differing in the relative amounts of reagents used. The Kagan protocol used a Ti(Oi-Pr)4 : (+)-diethyltartrate : tBuOOH :

water ratio of 1:2:1:1, whereas the Modena reagent utilized a ratio of 1:4:2:0. The results for the Kagan protocol are presented in table 8. Various other workers have attempted to use other chiral oxidation systems based on transition metal catalysts.[71] However, none of these systems have proved to be very versatile, the highest reported enantiomeric excess achieved to date being 70%.

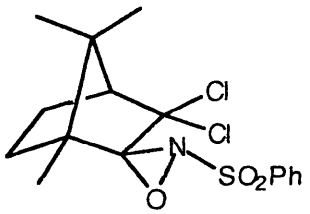


R^1	R^2	oxidant	yield %	%ee
pTol	Me	tBuOOH	90	89
"	Et	"	71	74
"	CH_2CO_2Me	"	81	64
o-anisyl	Me	"	58	86
2-napthyl	Me	"	88	90
"	nPr	"	78	24
2-pyridyl	Me	"	63	77
t-Bu	Me	"	72	53
p-Tol	Me	$PhC(Me)_2OOH$	-	96
o-anisyl	Me	"	-	93

Oxidation of prochiral sulphides utilizing the Kagan protocol.

Table 8

Another approach to the chiral oxidant has been explored by the Davis group.[72] Treatment of a range of sulphides (table 9) with the chiral oxaziridine (**51**) resulted in formation of sulphoxides in reasonable to high enantiomeric excesses.



(51)

R^1	R^2	%e.e
p-Tol	Me	95
"	n-Bu	90
"	i-Pr	95
Ph	vinyl	60
"	CH_2CO_2Me	65
t-Bu	Me	84

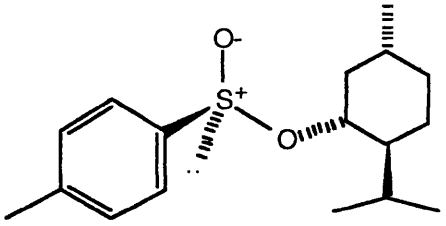
Oxidation of unsymmetrical sulphides with (51).

Table 9

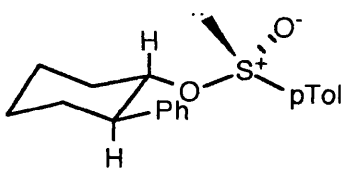
The biological oxidation of sulphides to sulphoxides has been recently comprehensively reviewed by Holland.[73] As a general rule enzymatic oxidations do not engender themselves to universal applicability, however, excellent results can be achieved with specific substrates.[74]

1.4. Improvements in Sulphoxide Sources.

The major drawback from the utilization of the sulphoxide sources based upon homochiral sulphinate esters (**25**) and (**28**) has been that after any asymmetric transformation, the next step in the synthetic sequence involved removal of the sulphoxide.



(25)



(28)

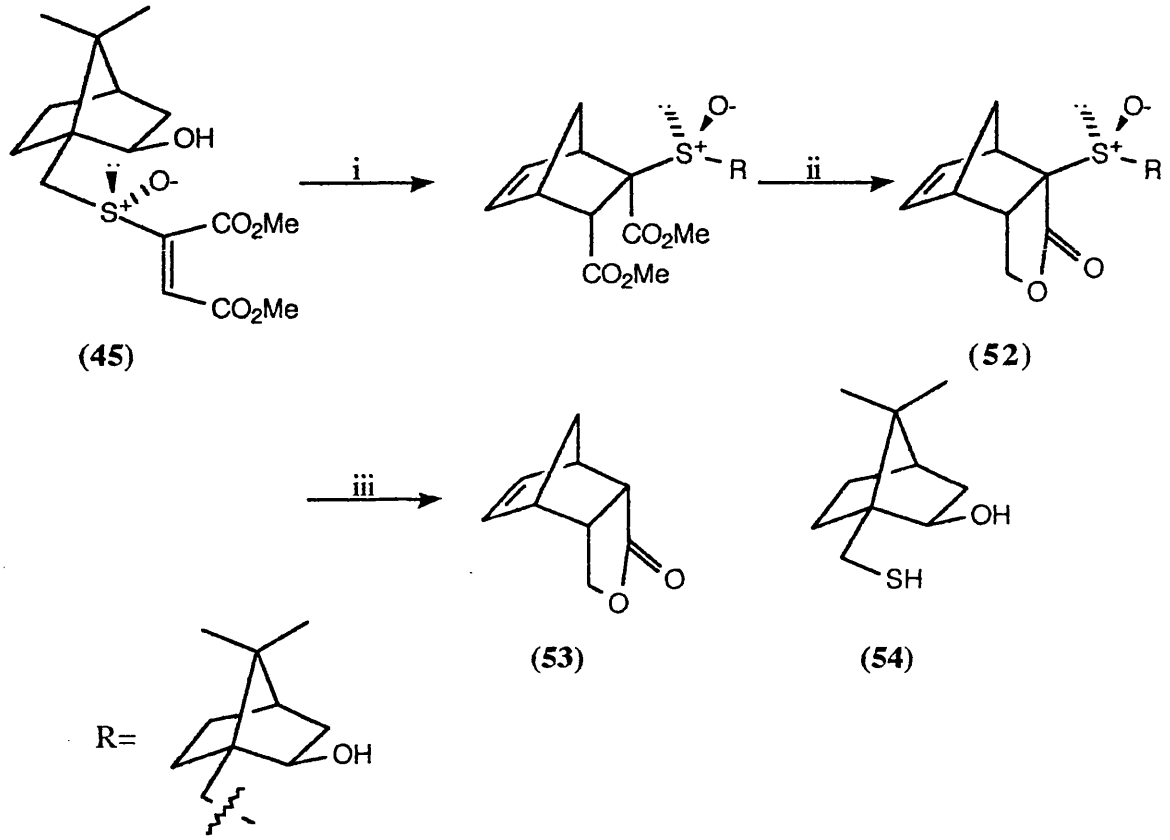
The removal of the sulphoxide necessitates the destruction of the hard won stereochemistry at the sulphur atom. This loss of stereochemical integrity lowers the overall usefulness of the sulphoxide stereodirecting methodology.

If an approach which retained the stereochemical information at sulphur within the spectator group could be developed this would represent an improvement in the sulphoxide methodology. The spectator group could "store" the stereochemical data either as an attribute of a single functional group, or within an intrinsic property of the spectator group.

1.4.1 Camphor based sulphoxides.

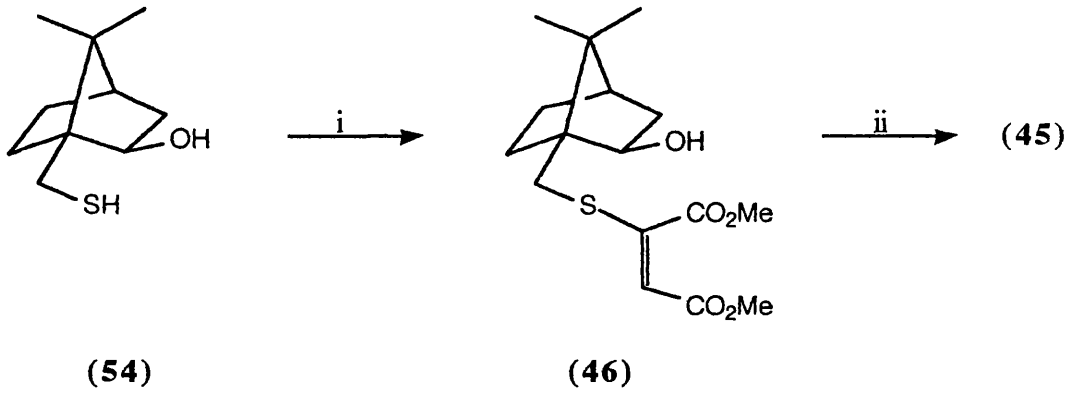
The camphor based sulphoxides described in 1.3.4. have the potential to be used as a recoverable source of chiral sulphoxide. The stereochemistry of the hydroxyl determines the resultant stereochemistry at the sulphoxide, *via* the directed oxidation of the sulphide. Therefore the regeneration of the sulphoxide is dependent upon the nature of a single functional group, namely the hydroxyl.

Koizumi[66] has utilized dimethyl-(d-isoborneol-10-sulphinyl)maleate (**45**) as a chiral dienophile in asymmetric Diels Alder reactions to synthesise homochiral bicyclo[2.2.1]heptane lactones (**52**). The next step in the synthetic sequence required the removal of the sulphinyl auxiliary. Treatment of (**52**) with samarium (II) iodide resulted in the formation of the lactone (**53**) and recovery of the auxiliary as the 10-mercaptoisoborneol (**54**) (Scheme 35). Thiol (**54**), upon treatment with dimethyl acetylene dicarboxylate generated the vinylsulphide (**46**), which underwent selective oxidation with *meta*-chloroperbenzoic acid resulting in the formation of the starting dienophile (**45**) (Scheme 36).



i Cyclopentadiene, zinc chloride, dichloromethane, ii Diisobutylaluminium hydride, toluene, iii Samarium (II) iodide, t-butanol, tetrahydrofuran.

Scheme 35

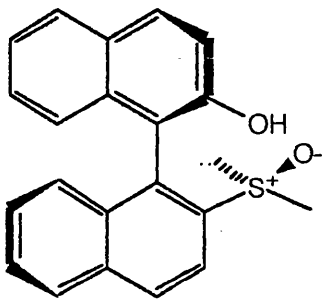


i Dimethylacetylenedicarboxylate, diphenylmethylphosphine, acetonitrile, ii *meta*-Chloroperbenzoic acid

Scheme 36

1.4.2 Binapthyl based systems.

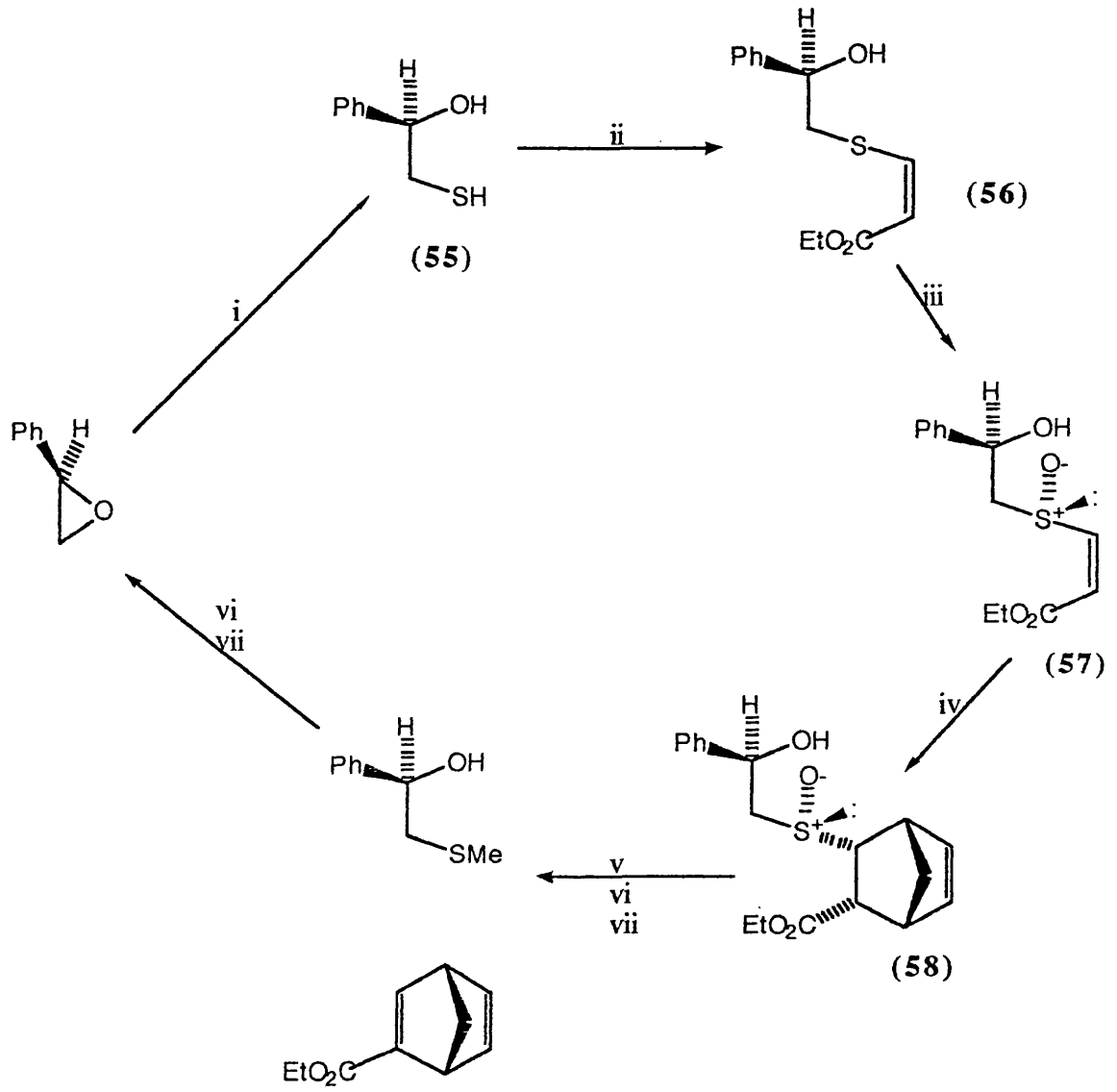
In essence the sulphoxides based upon the binapthyl system (such as (**49**)) would be expected to behave in the same fashion as the camphor systems. However, to date there is no report of such a system being used in this manner.



(**49**)

1.4.3 Epoxide based systems.

De Lucchi and co-workers have reported utilizing (R)-styrene oxide as a recoverable auxiliary[76] in the synthesis of optically active sulphinyl dienophiles. In this approach (Scheme 37) hydroxythiol (**55**), prepared by the method of Lalancette and Freche[77], was reacted with methyl propiolate to give the vinylsulphide (**56**) as a 4:1 mixture of double bond isomers. Hydroxyl directed oxidation of (**56**) with *meta*-chloroperbenzoic acid gave the vinylsulphoxide (**57**) in 70% diastereoisomeric excess. Diels Alder cycloaddition of (**57**) with cyclopentadiene resulted in a single stereoisomer of the cycloadduct (**58**). Tin (II) chloride elimination, followed by S-methylation and treatment with sodium hydroxide regenerates the (R)-styrene oxide. This again is an example of the "storage" of the sulphoxide stereochemistry within a single functional group in the spectator group.



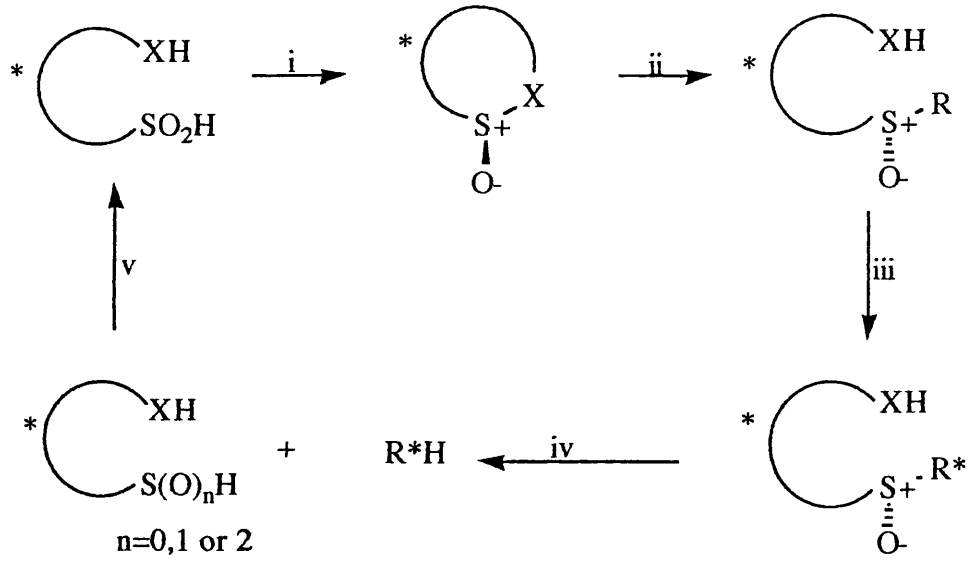
i Sulphur, sodium borohydride, followed by lithium aluminium hydride, ii Methyl propiolate, iii *meta*-Chloroperbenzoic acid, iv Cyclopentadiene, v Tin (II) chloride, acetyl chloride, vi Trimethyl oxonium tetrafluoroborate, vii Aqueous sodium hydroxide.

Scheme 37

1.5. Proposed Research.

The aim of the research undertaken was to develop a potential recyclable source of chiral sulphoxide which was readily synthesised from inexpensive starting materials. The functionalised chiral sulphoxides would be generated by nucleophilic reactions at an existing chiral sulphur centre as outlined in section 1.3.1.

It was envisaged that the leaving group would be connected to the spectator group and that the homochiral sulphoxide sulphur atom would be generated *via* a diastereoselective ring closure. The leaving group would cyclise, in such a sense, onto an activated sulphinic acid, with the selectivity controlled by an existing proximal chiral centre. The resultant cyclic sulphinamide or sulphinate would be able to undergo nucleophilic ring opening with inversion of stereochemistry at the sulphur atom (Scheme 38).



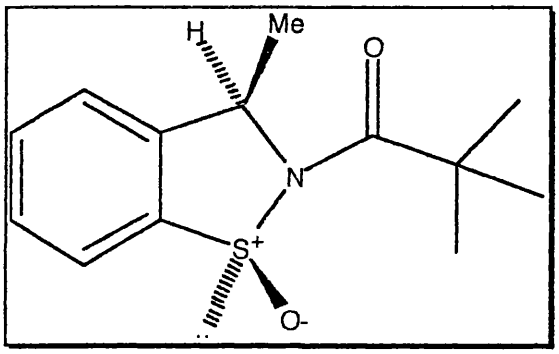
X=O or NHR
* existing chiral centre

i Diastereoselective ring closure, ii R-Metal, iii Asymmetric transformation, iv Reductive removal of R*H, v Oxidation.

Scheme 38.

Asymmetric transformation of the nucleophile followed by reductive removal of the sulphoxide would furnish the homochiral nucleophile and the sulphur residue. Transformation of the sulphur residue to the sulphinic acid would complete the regeneration cycle

Towards meeting the above aims the cyclic sulphinamide (**59**) was chosen as the initial substrate.

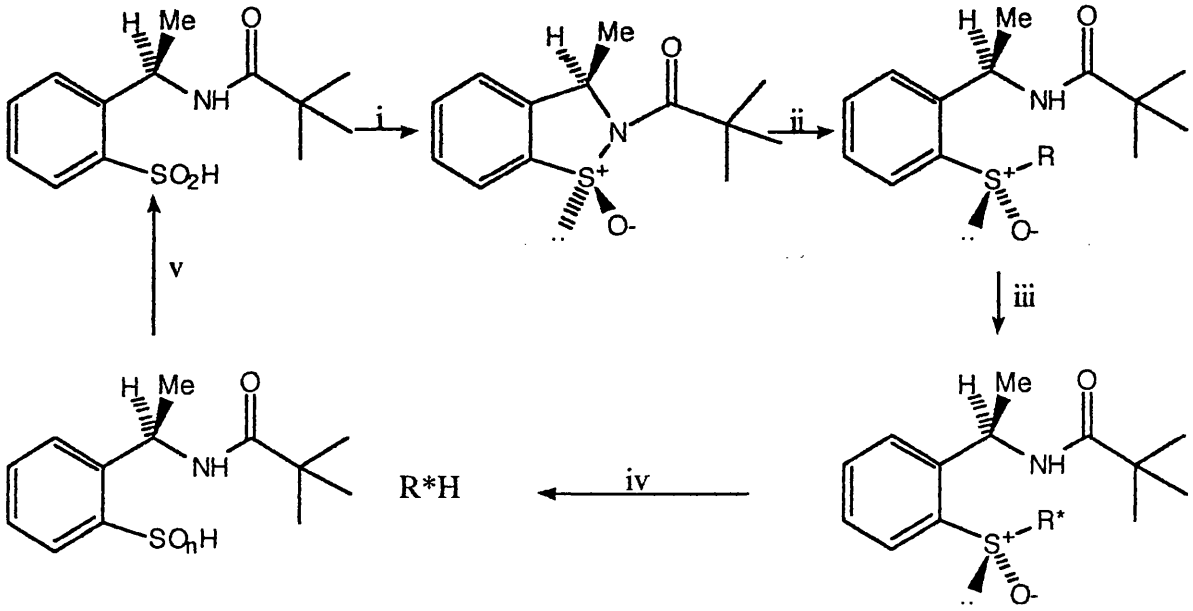


(**59**)

A substituted aromatic has been shown to be highly effective as a spectator group (see Section 1.3.2). The pivalamide would act as a ready leaving group, further activated by release of ring strain upon nucleophilic ring opening. The amide would also act as a nucleophile in the ring closure onto a sulphinyl chloride. Therefore the relationship between the amide side chain and the acid would have to be 1,2-substituted, so as to allow ring closure.

The existing chiral centre can be easily derived from α-methylbenzylamine which is commercially available in either enantiomeric form. It would be hoped that the proximal nature of the existing chiral centre to the amide nucleophile would effect the diastereoselective ring closure required to generate the chiral sulphur atom.

Further to a successful diastereoselective synthesis of the sulphinamide (**59**), nucleophilic ring opening reactions could be investigated. Upon successful ring opening asymmetric transformation routinely controlled by chiral sulphoxides could be investigated. The next stage in the synthetic sequence would be the attempt to regenerate the sulphinic acid from the sulphur residues generated in the reductive cleavage of the sulphoxide (Scheme 39).



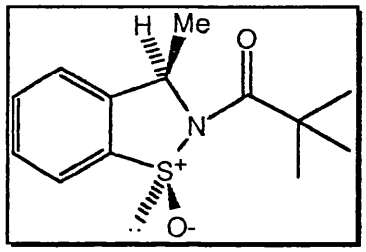
i Diastereoselective ring closure, ii Diastereoselective ring opening with R-Metal, iii Asymmetric transformation, iv Reductive removal of R*H, v Oxidation.

Scheme 39.

2.0 RESULTS AND DISCUSSION

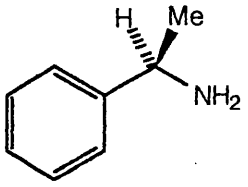
2.1 The Synthesis of the Cyclic Sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(59)

The starting point for the synthesis of sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) required a source of enantiomerically pure α-methyl benzylamine.



(**59**)

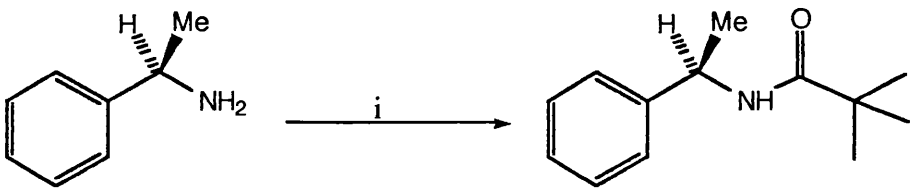
Enantiomerically pure α-methyl benzylamine, of either the (R)-(+)- and (S)-(-)-configuration, was commercially available at similar low cost.[78] The amine of (R)-(+)- configuration (**60**) was chosen as the starting point for the synthesis and shall be featured throughout the following discussions. The chemistry to be described could have as easily been performed on the amine of the (S)-(-)-configuration.



(R)-(+)-(**60**)

2.1.1 Synthesis of sulphinic acid (R)-(-)-(61)

Treatment of the commercially available (R)-(+)-(60) with trimethylacetyl chloride in the presence of triethylamine in dichloromethane resulted in the formation of crude amide (R)-(+)-(**62**). Recrystallization of crude (R)-(+)-(**62**) from a hexane dichloromethane mixture generated enantiomerically pure (R)-(+)-(**62**) in 80% yield (Scheme 40).

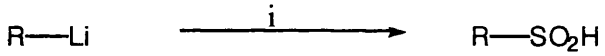


(R)-(+)-(**60**) (R)-(+)-(**62**)

i Trimethylacetyl chloride, triethylamine, dichloromethane.

Scheme 40

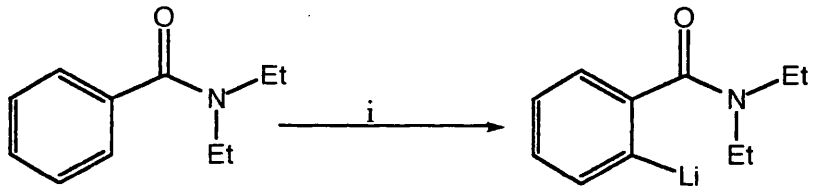
The next step in the synthesis of sulphinamide ($S_{(S)}R$)-(+)-(**59**) required the introduction of the sulphinic acid moiety. Reaction of an organolithium with gaseous sulphur dioxide has been reported to generate the required sulphinic acids (Scheme 41).[79]



i Sulphur dioxide, solvent.

Scheme 41

A method for generating the required organolithium was sought. Snieckus[80] has shown that in the presence of an amide side-chain an aromatic ring may be lithiated in the *ortho*-position by treatment with *sec*-butyllithium (Scheme 42).

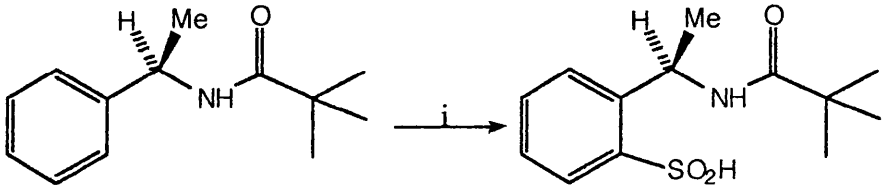


i *sec*-Butyllithium, TMEDA, tetrahydrofuran.

Scheme 42

With (R)-(+)-(**62**) more forcing conditions had to be applied since the *ortho*-proton was less activated due to the increased spatial distance and the reversed nature of the amide. Towards this end a diethyl ether solution of (R)-(+)-(**62**) was treated with two equivalents of *tert*-butyllithium (1.7 Molar in pentanes) in an attempt to effect the required lithiation and the subsequent aromatic anion reacted with gaseous sulphur

dioxide. Acid (R)-(-)-(**61**) was isolated in 95% yield after a base acid work-up (Scheme 43).

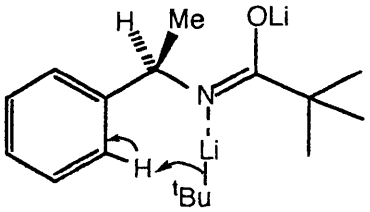


(R)-(+)-(**60**) (R)-(-)-(**61**)

i *tert*-Butyllithium (2 equivalents), diethyl ether, followed by sulphur dioxide.

Scheme 43

The deprotonated amide was thought to direct the lithiation of the aromatic ring *via* the intermediate shown in figure 6.



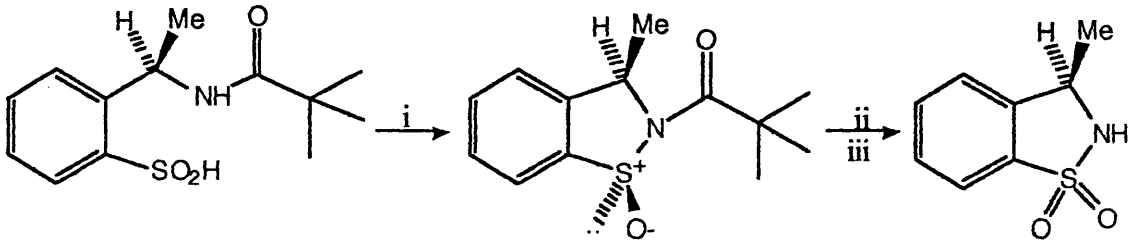
The intermediate for directed lithiation.

Figure 6

2.1.2. Cyclisation of sulphinic acid (R)-(-)-(**61**) to sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**)

The diastereoselective cyclisation of the amide nitrogen onto the activated sulphinic acid was to be the key step in the synthesis of ($S_{(S)}$ R)-(+)-*cis*-(**59**).

Sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) had been synthesised previously as an intermediate in the synthesis of sultam (R)-(+)-(**63**). In the reported cyclisation[81] (R)-(-)-(**61**) had been treated with thionyl chloride and triethylamine with subsequent deprotonation of the amide with sodium hydride causing diastereoselective ring closure. Oxidation of ($S_{(S)}$ R)-(+)-*cis*-(**59**) to the sulphone, followed by deprotection of the amide resulted in the formation of the sultam (R)-(+)-(**63**) (Scheme 44).



(R)-(-)-(**61**) ($S_{(S)}$ R)-(+)-*cis*-(**59**) (R)-(+)-(**63**)

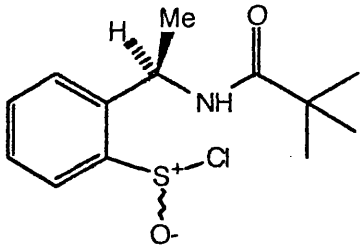
i Thionyl chloride, triethylamine; followed by sodium hydride, tetrahydrofuran,

ii Ruthenium (III) chloride, sodium periodate, acetonitrile, carbon tetrachloride, water,

iii Lithium hydroxide, hydrogen peroxide.

Scheme 44

In accordance with the reported synthesis of ($S_{(S)}$ R)-(+)-*cis*-(**59**), acid (**61**) was treated with thionyl chloride and triethylamine in tetrahydrofuran to generate the sulphinyl chloride (**64**). Treatment of (**64**) with sodium hydride resulted only in recovery of unreacted starting acid (**61**).

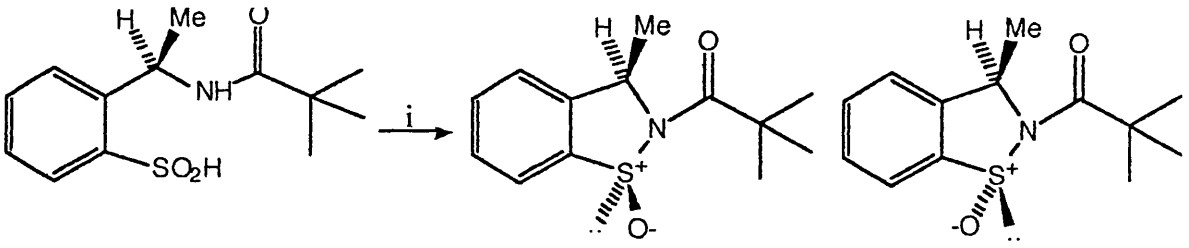


(**64**)

Repeated investigation of this route failed to generate the required (**59**) in greater than 5% chemical yield. To surmount this problem, a different approach to the cyclisation[82] of (**64**) was required.

Tertiary amine bases have been utilized in the cyclisations of diols and aminoalcohols with thionyl chloride to generate diastereoisomeric mixtures of cyclic sulphites and sulphinamides respectively (see Section 1.3.3 for examples). The examination of the possibility of utilizing such bases in the cyclisation of the chloride (**64**) to (**59**) was subsequently instigated.

The first study involved repeating the literature preparation of ($S_{(S)}$ R)-(+)-*cis*-(**59**) with a second portion of triethylamine replacing the sodium hydride. The initial result of this reaction was encouraging, since by examination of the crude reaction mixture *via* t.l.c, production of the required sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) had been achieved. However, upon isolation of the required material by flash column chromatography the resultant solid was found to consist of an epimeric mixture of *cis*-($S_{(S)}$ R)-(+)- and *trans*-($S_{(R)}$ R)-(**59**) (Scheme 45). The required ($S_{(S)}$ R)-(+)-*cis*-(**59**) was found, by comparison to the reported data, to be the major epimer. An investigation into other tertiary amine bases was then undertaken to determine if higher selectivity could be achieved (table 10).



(R)-(-)-(**61**) ($S_{(S)}$ R)-(+)-*cis*-(**59**) ($S_{(R)}$ R)-*trans*-(**59**)

i Tertiary amine (3 equivalents), thionyl chloride, tetrahydrofuran.

Scheme 45

Tertiary amine base	***Cis:Trans***	**Total yield %**
Triethylamine	6:1	63
Pyridine	3:2	60
4-Dimethylaminopyridine	>95:5	67

Comparison between the base used in cyclisation and the diastereoisomeric ratio of the corresponding reaction.

Table 10

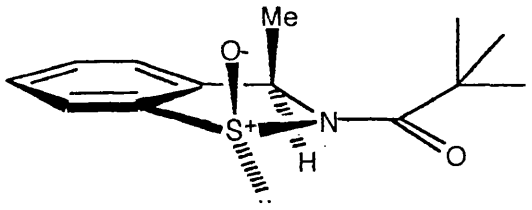
The arbitrary assignment of >95:5 arose from the fact that the ratios were determined by ^{1}H NMR spectroscopy and in the case of 4-dimethylaminopyridine only one signal corresponding to the *tert*-butyl protons resonance was observed.

From table 10 it can be seen that the optimum base for the cyclisation was 4-dimethylaminopyridine. Further attempts to optimize this reaction by variation of the reaction solvent, prolonging the reaction time and utilizing more base failed to increase the yield.

A successful synthesis of the cyclic sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) has been achieved in a total yield of 54% (from (R)-(+)-(**60**)) as the single *cis*-stereoisomer. The absolute and relative *cis*-stereochemistry (**59**) have been previously proven by single crystal X-ray determination.[81]

2.1.3 Rationale for selective ring closure.

From the structure derived from the reported[81] crystal structure, ($S_{(S)}$ R)-(+)-*cis*-(**59**) would appear to be the favoured thermodynamic relative configuration (figure 7).



Thermodynamically favoured configuration of ($S_{(S)}$ R)-(+)-*cis*-(59).

Figure 7

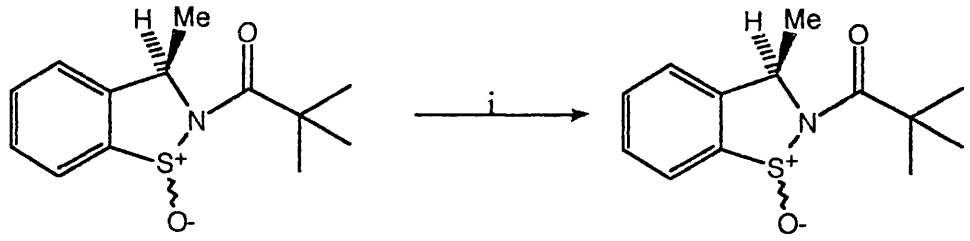
The dipoles arising from the carbonyl and sulphoxide were oriented away from each other minimizing any dipole-dipole interactions.[83] The ($S_{(S)}$ R)-(+)-*cis*-(**59**) product could be considered more stable because the methyl, pivaloyl and sulphur oxygen were orientated pseudo-*trans* thereby minimizing unfavourable steric interactions.

In an attempt to determine whether the cyclisation to ($S_{(S)}$ R)-(+)-*cis*-(**59**) was occurring under thermodynamic equilibrium control (generating the thermodynamic product), two experiments were undertaken.

If an equilibrium occurred in the selective ring closure, treatment of an epimeric mixture of (**59**) with 4-dimethylaminopyridine would result in the formation of the diastereoisomerically pure ($S_{(S)}$ R)-(+)-*cis*-(**59**). By the corollary, treatment of

diastereoisomerically pure ($S_{(S)}$ R)-(+)-*cis*-(**59**) with triethylamine would generate a 6:1 epimeric mixture of *cis* :*trans*-(**59**).

The treatment of the 6:1 epimeric mixture (derived from the triethylamine experiment) with 4-dimethylaminopyridine in tetrahydrofuran for 16h resulted in no change in the diastereoisomeric ratio (Scheme 46).

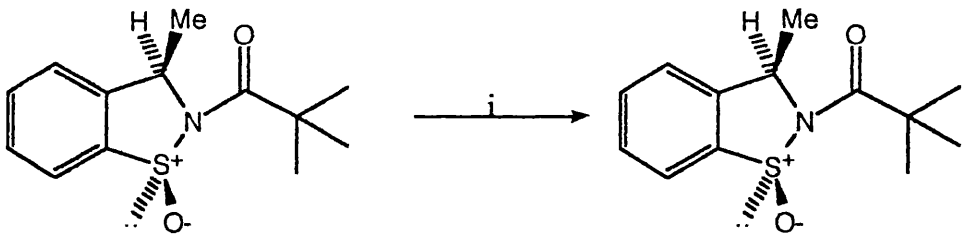


6:1 6:1

i 4-Dimethylaminopyridine, terahydrofuran, 16h.

Scheme 46

In the second investigative reaction, diastereoisomerically pure ($S_{(S)}$ R)-(+)-*cis*-(**59**) was treated with triethylamine under the standard reaction conditions. Examination of the crude reaction mixture by ^1H NMR spectroscopy showed only ($S_{(S)}$ R)-(+)-*cis*-(**59**) (Scheme 47).



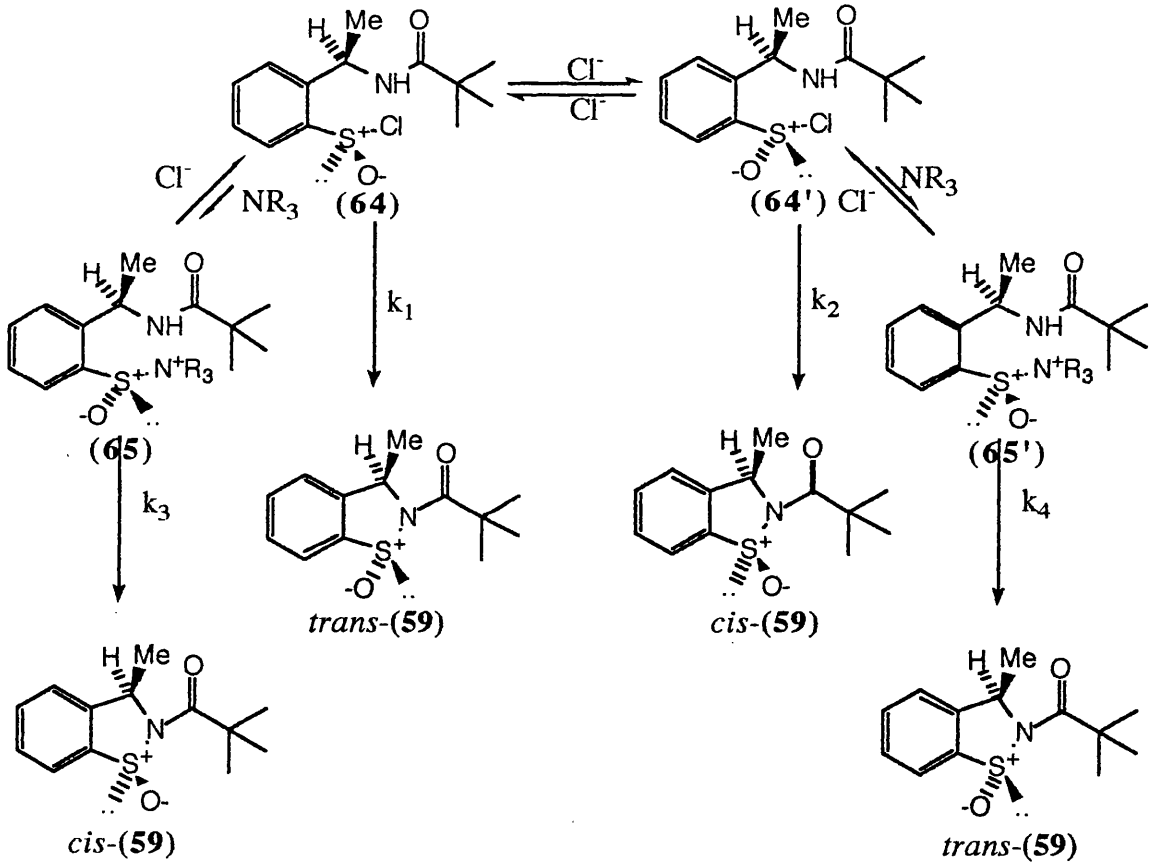
i Triethylamine, tetrahydrofuran, 16h.

Scheme 47

From the data derived above, the reaction control cannot be due to any thermodynamically equilibrating ring closure, but must occur through an irreversible ring closure.

The range of selectivities observed in the cyclisation reaction must be a consequence of the leaving group abilities of the amines used. Initial reaction of the acid (R)-(-)-(**61**) with thionyl chloride would result in the formation of an epimeric pair of sulphinyl

chlorides (**64**) and (**64'**). The diastereoisomeric (**64**) and (**64'**), after sodium hydride promoted amide deprotonation, would cyclise at differing rates such that ($S_{(S)}$R)-(+)-*cis*-(**59**) was formed in excess. Replacement of sodium hydride with the tertiary amine bases caused a change in the mechanism. Addition of the amine resulted in the formation of a low concentration of the highly reactive ammonium sulphinates (from (**64**) and amine[84]) (**65**) and (**65'**) which underwent cyclisation at faster rates than (**64**) and (**64'**) thereby dominating the observed selectivity. From the results achieved, for pyridine $k_4=k_3$, $k_4>k_3$ for triethylamine, and for 4-dimethylaminopyridine $k_4 \gg k_3$ (Scheme 48). The pK_a differences[85] between pyridine (5.21), triethylamine (11.01) and 4-dimethylaminopyridine (9.65) may give an insight into the poor selectivity observed with pyridine. A low pK_a would suggest a good leaving group which would be less sensitive to the structure of the cyclisation transition state, hence reducing the selectivity.



Proposed mechanism for formation of ($S_{(S)}$ R)-(+)-*cis*-(59).

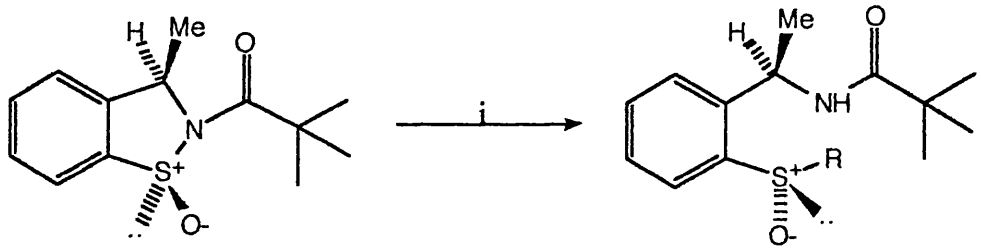
Scheme 48

The reason for the increased selectivity of 4-dimethylaminopyridine over triethylamine was unclear. From the pK_a argument, triethylamine would be more selective. However, 4-dimethylaminopyridine is more nucleophilic in nature than the trialkylamine, making it a very poor leaving group. This fact may override the difference in pK_a hence giving the selectivity observed with 4-dimethylaminopyridine.

2.1.4 Stability of the sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**).

The sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) exists as a stable crystalline solid which has been stored for six months with no decomposition. The sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) was readily hydrolyzed to give the expected sulphinic acid (R)-(-)-(**61**) in either acidic or basic aqueous conditions.

Treatment of ($S_{(S)}$ R)-(+)-*cis*-(**59**) with a range of simple nucleophiles was subsequently examined. With the exception of sodium methoxide, these nucleophilic reactions resulted in attack at the sulphur atom generating a single diastereoisomer, as determined by ^1H NMR spectroscopy (Scheme 49 and table 11).



($S_{(S)}$ R)-(+)-*cis*-(**59**)

i R-Metal, solvent, temperature (see table 11).

Scheme 49

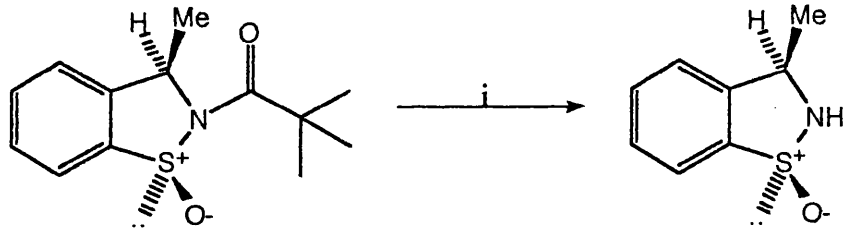
Authentic samples of each diastereoisomer were prepared by the reaction of an epimeric sample of ($S_{(S)}$ R)-(+)-*cis*-(**59**) (derived from the triethylamine reaction) with the relevant nucleophiles.

R	Metal	Temperature °C	Solvent	Yield %
Methyl	MgBr	-78	diethyl ether	84
Methyl	Li	-78	diethyl ether	88
n-Butyl	Li	-78	tetrahydrofuran	70
Methoxy	Li	0	tetrahydrofuran	64
t-Butyl[86]	Li	-78	tetrahydrofuran	57
Benzyl[86]	MgBr	-78	diethyl ether	89

Nucleophilic ring opening of ($S_{(S)}$ R)-(+)-*cis*-(59)

Table 11

Treatment of ($S_{(S)}$ R)-(+)-*cis*-(**59**) with sodium methoxide (generated from sodium hydride and methanol) in tetrahydrofuran resulted in the removal of the trimethylacetyl group from the nitrogen, generating the cyclic sulphinamine ($S_{(S)}$ R)-(+)-*cis*-(**66**) in 78% yield (Scheme 50).



($S_{(S)}$ R)-(+)-*cis*-(**59**) ($S_{(S)}$ R)-(+)-*cis*-(**66**)

i Sodium methoxide, tetrahydrofuran.

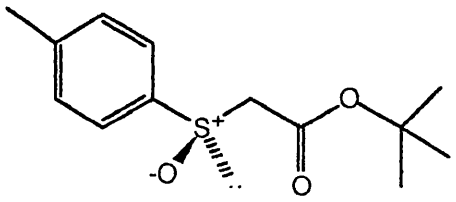
Scheme 50

2.2 Aldol Chemistry.

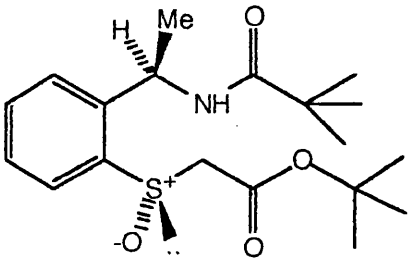
With the successful synthesis of the sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) achieved, an area of sulphoxide mediated chemistry was targeted in an attempt to assess the synthetic utility of ($S_{(S)}$ R)-(+)-*cis*-(**59**) as a source of homochiral sulphoxide for asymmetric processes.

2.2.1 Synthesis of sulphinylacetate ($S_{(S)}$ R)-(-)-(**67**).

The first investigation focused on the synthesis of enantiomerically enriched β-hydroxyesters, *via* the aldol reaction of sulphinyl acetate ($S_{(S)}$ R)-(-)-(**67**) with a variety of aldehydes. The chemistry of structurally related acetate[87] (**68**), derived from (**25**), has already been discussed.[29] With the data from the reactions of (**68**) in hand a means of assessing the efficiency of functionalised sulphoxides derived from ($S_{(S)}$ R)-(+)-*cis*-(**59**) was available.

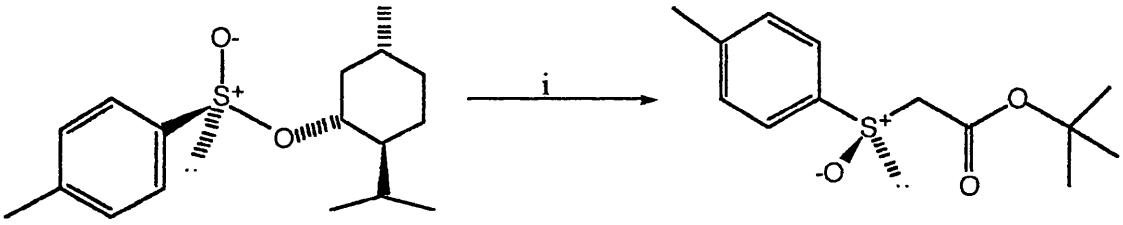


(**68**)



($S_{(S)}$ R)-(-)-(**67**)

The first stage in the examination of the aldol chemistry involved the synthesis of ($S_{(S)}$ R)-(-)-(**67**). In the related synthesis of (**68**) treatment of (**25**) with the magnesium bromide enolate of *tert*-butyl acetate had been reported[87] to generate the required compound in 90% yield (Scheme 51).



(**25**) (**68**)

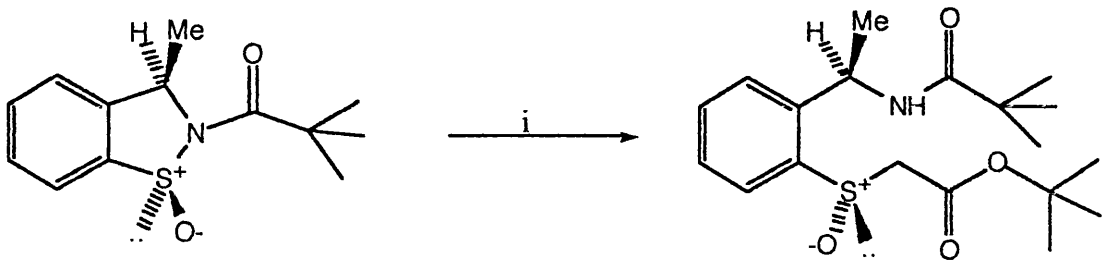
90%

i *tert*-Butyl acetate, magnesium bromide diisopropylamide, diethyl ether.

Scheme 51

In accordance with the literature procedure, *tert*-butyl acetate was treated with magnesium bromide diisopropylamide (generated from ethyl magnesium bromide and diisopropylamine) to generate the corresponding ester enolate, and the enolate

subsequently reacted with ($S_{(S)}$ R)-(+)-*cis*-(**59**). Sulphinyl acetate ($S_{(S)}$ R)-(-)-(**67**) was isolated after column chromatography in 87% yield as a stable crystalline solid (Scheme 52).



($S_{(S)}$ R)-(+)-*cis*-(**59**) ($S_{(S)}$ R)-(-)-(**67**)

87%

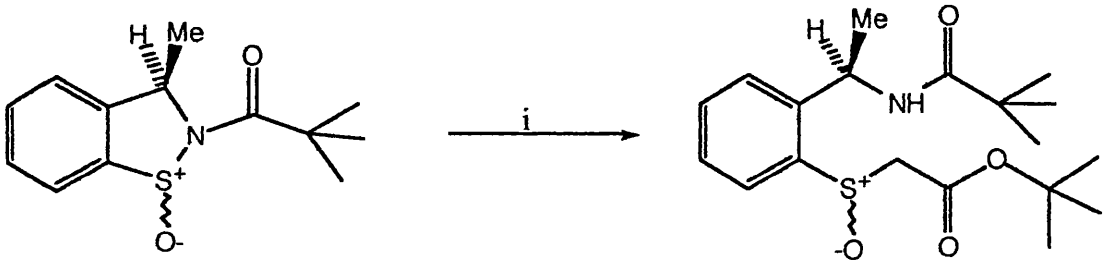
i *tert*-Butyl acetate, magnesium bromide diisopropylamide, diethyl ether.

Scheme 52

The crystallinity of the sulphinylacetate ($S_{(S)}$ R)-(-)-(**67**) represented a significant practical advantage over the methodology based on (**25**) since (**68**) existed as a viscous oil, and hence was not easily handled.

Compound ($S_{(S)}$ R)-(-)-(**67**).was shown to be a single diastereoisomer by ^1H NMR spectroscopy. The presence of the fixed stereocentre derived from (R)-(+)-(**60**) caused all compounds to be diastereoisomers where the sulphur atom was asymmetrically substituted. The existence of ($S_{(S)}$ R)-(-)-(**67**) as a diastereoisomer represented a second advantage over (**68**) since (**68**) exists as an enantiomer and complex ^1H NMR spectroscopic chiral shift techniques are required to check its stereochemical purity. The purity of ($S_{(S)}$ R)-(-)-(**67**) could be assessed by simple ^1H NMR spectroscopy.

To confirm the diastereoisomeric purity of ($S_{(S)}$ R)-(-)-(**67**) a known epimeric mixture (3:2) of (**59**) was treated with the magnesium bromide enolate of *tert*-butyl acetate (Scheme 53).



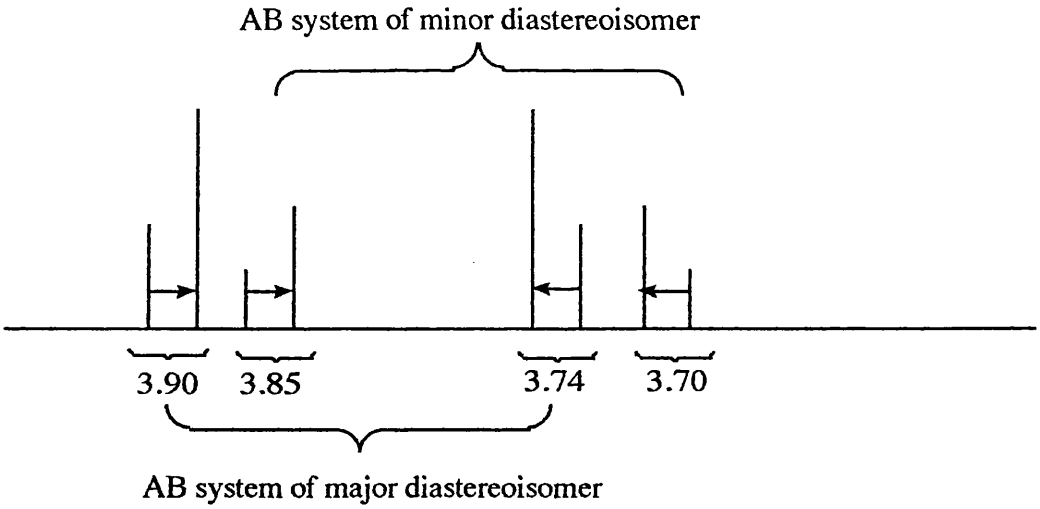
(59) **(67)**

3:2 3:2

i *tert*-Butyl acetate, magnesium bromide diisopropylamide, diethyl ether.

Scheme 53

Examination of the resultant crude (after removal of excess *tert*-butyl acetate by flash column chromatography) reaction mixture by ^1H NMR spectroscopy revealed the presence of distinct proton resonance signals corresponding to each epimer (an example of this is illustrated in figure 8).

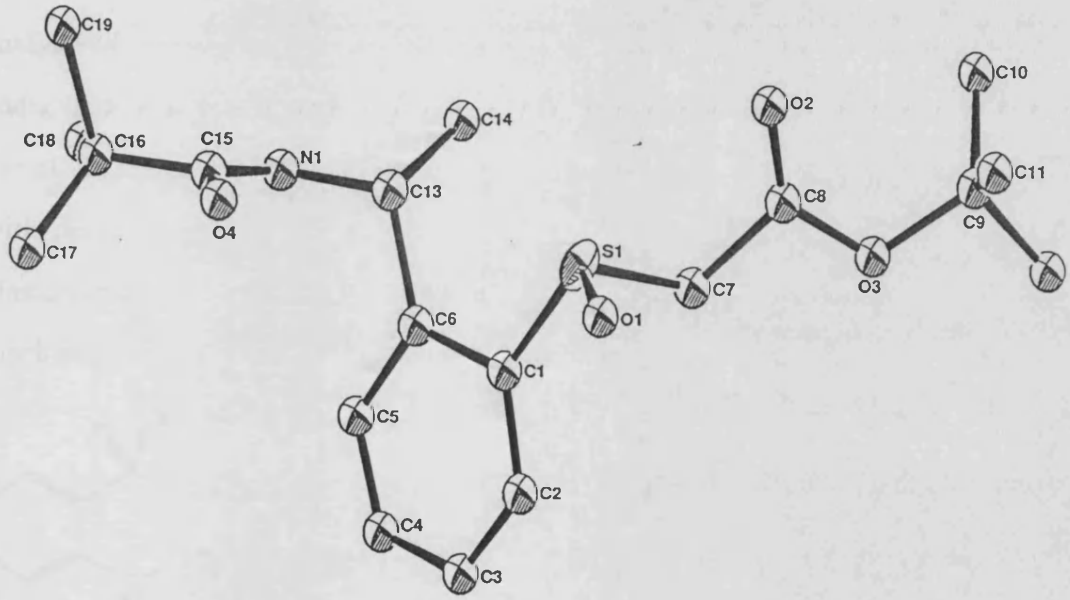


A representation of the methylene proton resonances in the epimeric mixture of sulphinylacetates (67). The AB system at 3.90 and 3.74ppm corresponds to that achieved with diastereoisomerically pure ($S_{(S)}$ R)-(+)-*cis*-(59).

Figure 8

The epimeric ratio of the sulphinyl acetates corresponded exactly with that of the starting sulphinamide.

As confirmation that inversion of stereochemistry at sulphur had occurred in the reaction to generate diastereomerically pure ($S_{(S)}$ R)-(-)-**(67)**, a single crystal structure determination was undertaken. From the structure obtained, the correct relative stereochemistry between the α-methyl and the sulphoxide was observed. Since the absolute stereochemistry at the benzylic position was known, the absolute stereochemistry could be determined. The result of this X-ray study showed unambiguously that inversion of configuration at sulphur had occurred (figure 9).

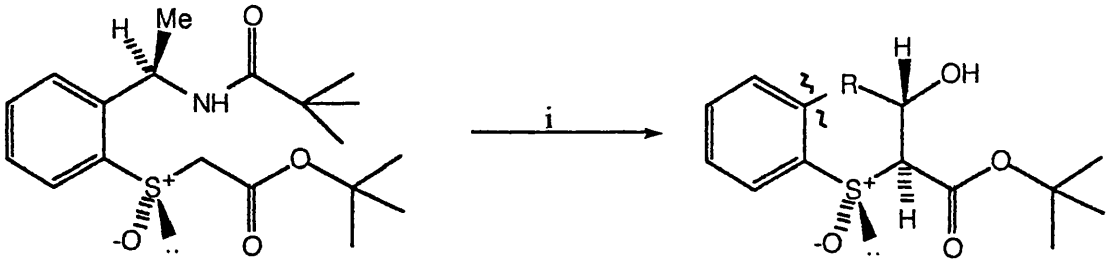


X-ray structure of sulphinyl acetate ($S_{(S)}$ R)-(-)-(67).

Figure 9.

2.2.2 Reaction of sulphinylacetate ($S_{(S)}$ R)-(-)-(**67**).with aldehydes.

With the synthesis of ($S_{(S)}$ R)-(-)-(**67**) achieved, the subsequent reaction between the enolate of ($S_{(S)}$ R)-(-)-(**67**) and a series of aldehydes could be studied. The deprotonation of ($S_{(S)}$ R)-(-)-(**67**) was carried out with *tert*-butyl magnesium bromide in tetrahydrofuran solution, in accordance with the precedent set by the analogous reactions utilizing (**68**). The aldehyde was added to deprotonated ($S_{(S)}$ R)-(-)-(**67**) at -78°C and the reaction mixture stirred at this temperature for 6h, then allowed to warm to room temperature and stirring continued for a further 6h (Scheme 54). The reactions were quenched under neutral conditions (saturated aqueous ammonium chloride) and excess aldehyde removed by column chromatography. ^{1}H NMR spectroscopic analysis of the resultant crude product showed that a single diastereoisomer of aldol adduct (**69**) had been formed (table 12) in all but one of the aromatic examples The use of aliphatic aldehydes gave products of decreasing diastereoisomeric selectivity with decreasing size of the alkyl group. With the examples of low selectivity, diastereoisomerically pure products could be isolated *via* recystallisation, albeit at a much reduced chemical yield.



($S_{(S)}$ R)-(-)-(**67**) (**69**)

i *tert*-Butylmagnesium bromide, RCHO, tetrahydrofuran, -78°C for 6h, followed by 6h at ambient temperature.

Scheme 54

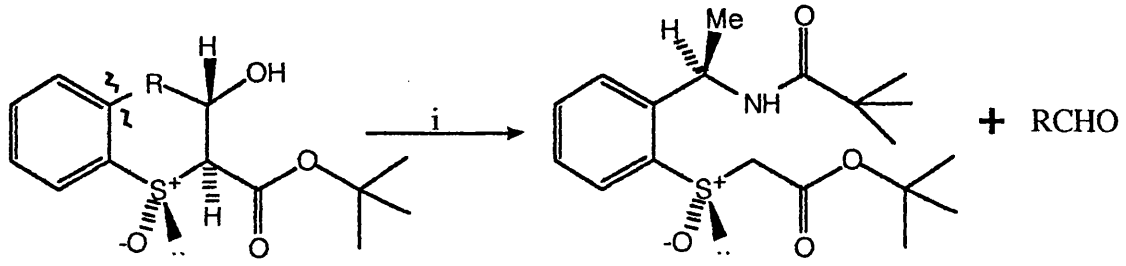
Product (69).	R	Yield %	d.e.%
a	Ph	75	>92
b	4-Methoxyphenyl	70	>92
c	3-Methoxyphenyl	80	>92
d	2-Methoxyphenyl	90	33
e	4-Nitrophenyl	70	>92
f	2-Nitrophenyl	80	>92
g	*tert*-Butyl	90	>92
h	*iso*-Propyl	75	75
i	Methyl	60	50

The reaction of aldehydes with the magnesium bromide enolate of $(S_{(S)}$ R)-(-)-(67).

Table 12

Measurement of ratios of up to 25:1 were possible using ^{1}H NMR spectroscopy, hence the arbitrary assignment of >92% diastereoisomeric excess when only the one isomer was detected.

In an attempt to determine the relative configurations in the products, (**69a**) was subjected to single crystal structure determination. However, aldol products (**69**) decomposed in the X-ray beam. Products (**69a-i**) were shown to be unstable under high energy conditions by observing their behaviour in mass spectroscopy. In both the electron (E.I.) and chemical ionization (C.I) modes the only fragments observed in the spectra were those corresponding to the retro-aldol products (Scheme 55).



(**69**) ($S_{(S)}$ R)-(-)-(**67**)

i E.I or C.I.,

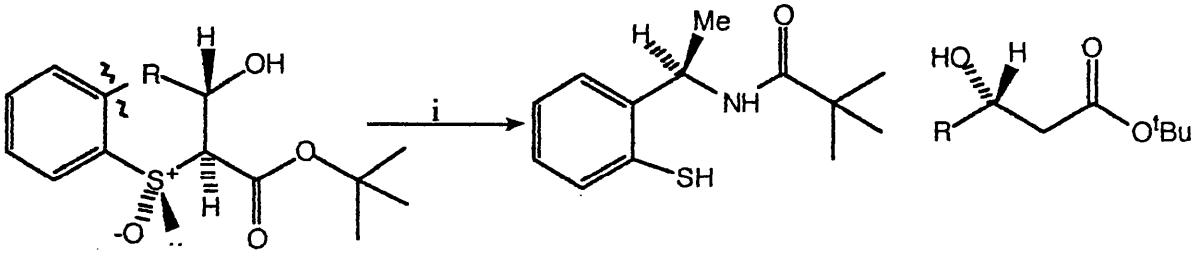
Scheme 55

Only when the "softer" fast atom bombardment (F.A.B.) technique was utilized were molecular ions corresponding to the required products (**69a-i**) observed.

2.2.3 Assignment of relative stereochemistry by chemical means.

Since X-ray studies were unable to ascertain the relative configuration of the products (**69**), chemical studies to determine the configurations were undertaken. Towards this end, a representative number of the aldol adducts (**69**) were subjected to the aluminium amalgam[17] cleavage conditions (Scheme 56). The investigation also allowed for the determination of the epimeric position in the adducts (**69d, h, i**) of low diastereoisomeric excess, since in (**69**) two new stereocentres were simultaneously generated.

Treatment of the aldol adducts (**69**) with aluminium amalgam[17] in 10% aqueous tetrahydrofuran caused the cleavage of the C_{alkyl}-S bond leading to the formation of thiol (R)-(+)-(**70**) and the required β-hydroxyester (**71**) (Scheme 56 and table 13). Treatment of (**71**) with the chiral shift reagent tris[3-(heptafluoropropylhyroxymethylene)-(+)-camphorato]europium (III) (**72**) was used for the determination of the enantiomeric purity of β-hydroxyesters (**71**)



(69) (R)-(+)-(70) (71)

i Aluminium amalgam, 10% aq. tetrahydrofuran, 16h.

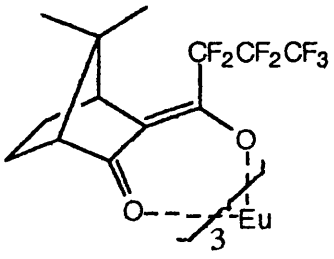
Scheme 56

Aldol adduct	Yield of (71)	e.e % of (71)[a]	Yield of (70)
(69a)[b].	85	>92	80
(69f)[b].	65[e]	>92	-
(69d)[c].	68	33	-
(69h)[d]	75	75	73

a Determined by ^1H NMR techniques; b. Diastereoisomerically pure; c. 33% diastereoisomeric excess; d. 75% diastereoisomeric excess; e Reduction to the primary amine.

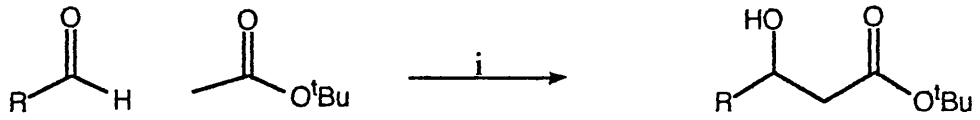
Reductive cleavage of a representative sample of aldol adducts (69).

Table 13



(72)

Addition of *ca.* 0.2 equivalents of shift reagent (72) to a deuterochloroform solution of racemic β-hydroxyester (generated *via* the route illustrated in scheme 57[88] and table 14) resulted in the splitting to base line resolution (table 15) of the *tert*-butyl signal corresponding to each enantiomer.



(±)-(**71**)

i Lithium diisopropylamide, -78°C, tetrahydrofuran.

Scheme 57

R	Yield %
Phenyl (**71a**)	73
2-Methoxyphenyl (**71b**)	60
iso-Propyl (**71c**)	75
2-Nitrophenyl (**71d**)	49

The synthesis of racemic β-hydroxyesters (71) for chiral shift purposes.

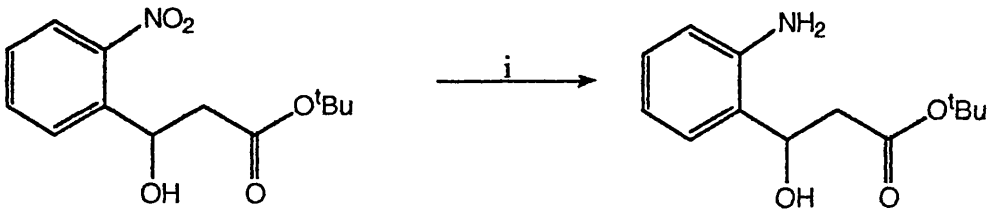
Table 14

R	Racemic resonances for *tert*-butyl protons	Cleaved product resonances for *tert*-butyl protons
Phenyl (**71a**)	1.77 and 1.71	1.70
2-Aminophenyl (**71e**)	1.66 and 1.63	1.66
2-Methoxyphenyl (**71b**)	1.84 and 1.77	1.84 (1):1.77 (3)
iso-Propyl (**71c**)	1.85 and 1.77	1.85 (7):1.77 (1)

^{1}H NMR spectroscopic data for β-hydroxyesters (71).

Table 15

The cleavage of the adduct derived from 2-nitrobenzaldehyde (**69f**) resulted in the concomitant reduction of the aromatic nitro group to the primary aromatic amine (**71e**).[89] An authentic sample of racemic (**71e**) was synthesized *via* the reduction of racemic nitro-β-hydroxyester (**71d**) in 77% yield (Scheme 58).



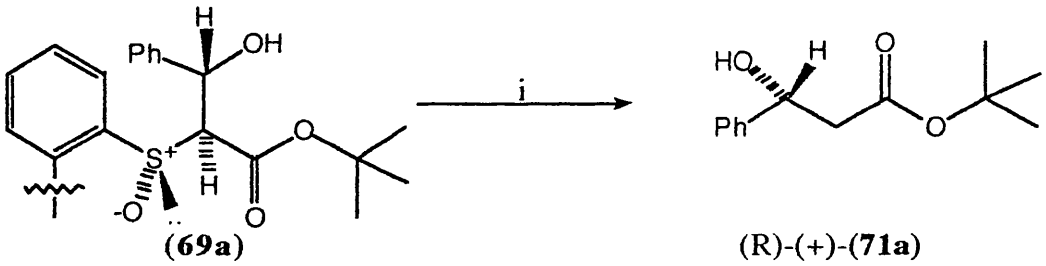
(±)-(**71d**) (±)-(**71e**)

i Aluminium amalgam, 10% aqueous tetrahydrofuran, 16h.

Scheme 58

Adduct (**69a**), derived from benzaldehyde, was cleaved to aid the assignment of the absolute stereochemistry at the β-position of the adduct. The rotation of β-hydroxyester (**71a**) generated in the cleavage had an optical rotation of +13° (c=0.15, ethanol). From the previous work,[29] the optical rotation of the (S)-β-hydroxyester had been reported as having a value of -9.1° (c=2.46, ethanol).

β-Hydroxyester (**71a**) synthesized in the reductive cleavage from aldol adduct (**69a**) could be confidently assigned the (R)-configuration (Scheme 59).



(**69a**) (R)-(+)-(**71a**)

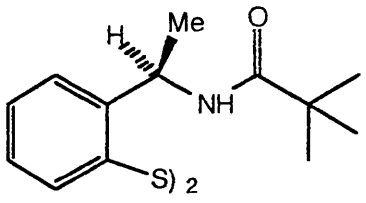
[α] = +13° (c=0.15, ethanol)

i Aluminium amalgam, 10% aqueous tetrahydrofuran, 16h.

Scheme 59

Cleavage of epimeric adducts (**69d**) and (**69h**) showed that the epimeric position existed at the β-position, since the enantiomeric excesses of the β-hydroxyesters corresponded exactly to the starting adducts diastereoisomeric excesses (entries 3 and 4 in table 13).

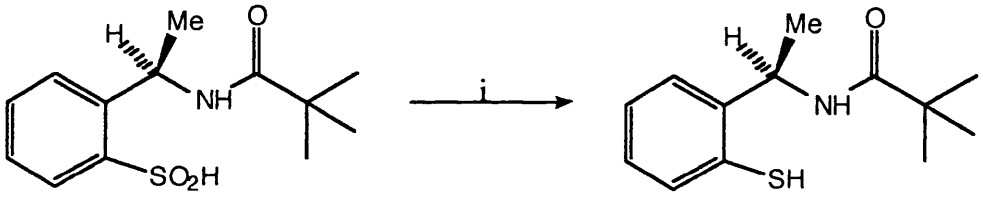
Disulphide (R)-(**73**) was initially thought to constitute the sulphur containing reduction product , this was later proved to be the result of aerial oxidation of thiol (R)-(+)-(**70**).



(R)-(**73**)

The recovery of (R)-(+)-(**70**) as the sulphur component was the first recorded report of the nature of the sulphoxide auxiliary after reductive cleavage.

An authentic sample of thiol (R)-(+)-(**70**) was prepared for comparison by the reduction, using triphenylphosphine-iodine[90], of the sulphinic acid (R)-(-)-(**61**) (Scheme 60).



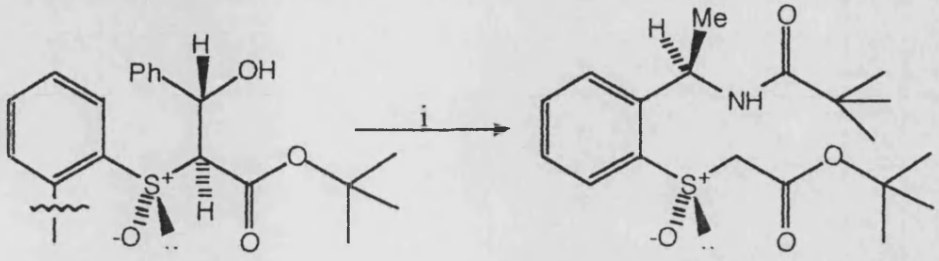
(R)-(-)-(**61**) (R)-(+)-(**70**)

i Triphenylphosphine, iodine, toluene, chloroform.

Scheme 60

2.2.4. Rationale for results.

The use of *tert*-butyl magnesium bromide as base in the aldol reaction proved to be of extreme importance. Treatment of the sodium enolate of ($S_{(S)}$ R)-(-)-(**67**) with an aldehyde resulted in the recovery of unreacted starting materials. The lack of reactivity of the sodium enolate can be explained by proposing that reaction was totally reversible, hence no generation of products. To confirm that a retro-aldol reaction could occur under lithium enolate conditions, adduct (**69a**) was treated with either lithium diisopropylamide or *tert*-butyl lithium at -78°C. The result of the reaction was the expected retro-aldol, giving sulphinyl acetate ($S_{(S)}$ R)-(-)-(**67**) (Scheme 61).



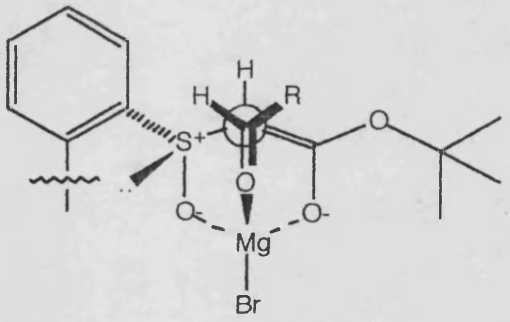
(69a) $(S_{(S)}$ R)-(-)-**(67)**

i Lithium diisopropylamide, or t-butyllithium, tetrahydrofuran, -78°C.

Scheme 61

The more covalent oxygen-magnesium bond was required to prevent any retro-aldol reaction. The magnesium counter-ion has the additional ability to form a strongly chelated intermediate (figure 9) which again prevents the reverse reaction.

The high selectivity observed in the reaction between the magnesium enolate of $(S_{(S)}$ R)-(-)-**(67)** and the aldehydes could also be explained using the highly chelated transition state illustrated in figure 9.



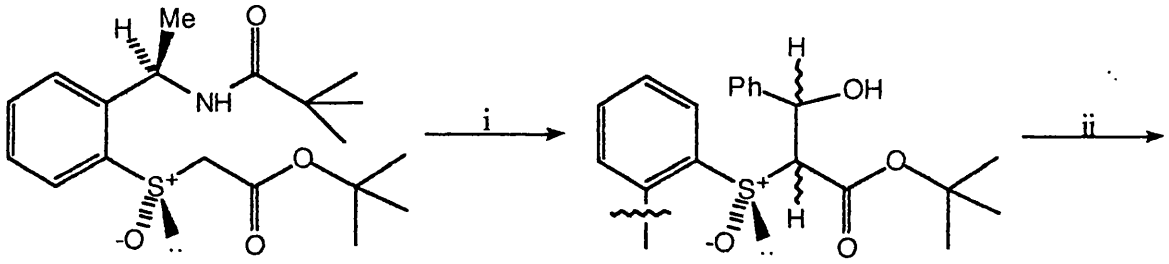
The chelated transition state proposed for the aldol reaction.

Figure 9

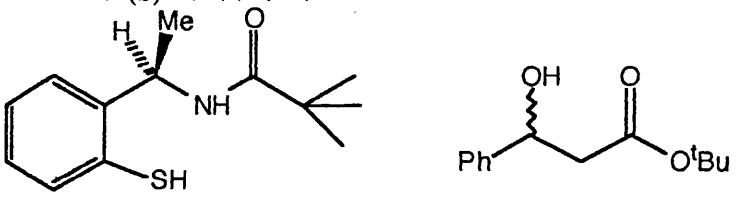
The strongly coordinating magnesium counter-ion bound both the oxygens of the sulphoxide and the enolate tightly to the metal and the incoming aldehyde was delivered, *via* coordination of the magnesium to the carbonyl oxygen, to the less sterically hindered face of the enolate (the face away from the bulky aromatic residue). The R-group on the aldehyde was orientated away from the sterically demanding aromatic residue.

The authenticity of the transition state could be validated by comparing the relative stereochemistry of the formed β-stereocentre in (**69**) with that of the sulphoxide stereocentre. The reported[28] data stated that the (R)-configuration of the sulphoxide in (**68**) gave rise to β-hydroxyesters of the (S)-configuration. With ($S_{(S)}$ R)-(-)-(**67**), the (S)-configuration at sulphur generated (R)-β-hydroxyesters, hence the same relative configuration between the sulphoxide and the β-centre was achieved in each case. The transition state for explaining the selectivity observed with ($S_{(S)}$ R)-(-)-(**67**) fitted the reported model.[29]

In seeking further explanations for the observed selectivities, a series of experiments were devised to determine whether kinetic or thermodynamic control predominated. Treatment of ($S_{(S)}$ R)-(-)-(**67**) with *tert*-butyl magnesium bromide at -78°C generated the enolate in the usual fashion. Reaction of the enolate with benzaldehyde, followed (Scheme 62) by quenching after 6h at -78°C resulted in the formation of a 1:1 diastereoisomeric mixture, as determined by ^{1}H NMR spectroscopic analysis, of adduct (**69a**).



($S_{(S)}$ R)-(-)-(**67**) (**69**)



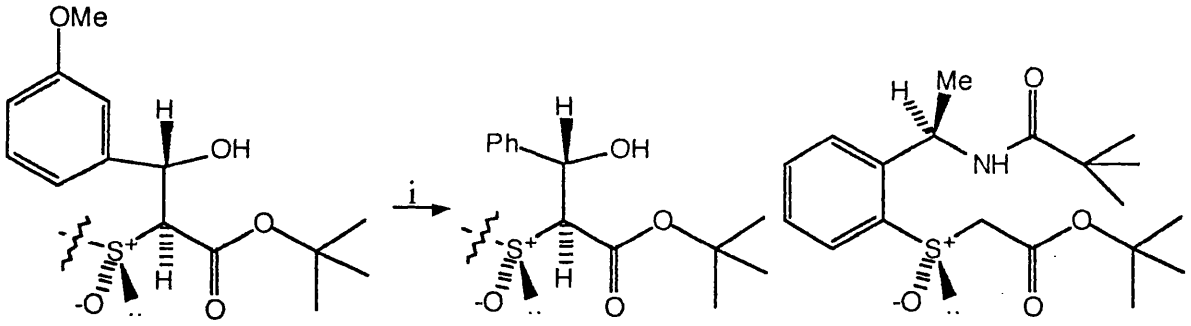
(R)-(+)-(**70**) (±)-(**71**)

i *tert*-Butyl magnesium bromide, followed by benzaldehyde, tetrahydrofuran, -78°C, 6h, ii Aluminium amalgam, 10% aq. tetrahydrofuran.

Scheme 62

Aluminium amalgam cleavage of the crude reaction mixture generated β-hydroxyester (**71a**) as a racemate, determined by chiral shift reagent (**72**), in 80% yield. The epimeric position in adduct (**69a**) was then confidently assigned to the the carbon bearing the hydroxyl group.

Deprotonation of diastereoisomerically pure adduct (**69c**) in tetrahydrofuran at -78°C was achieved with *tert*-butyl magnesium bromide. The resultant reaction mixture was treated with benzaldehyde and the reaction stirred at this temperature for 6h, followed by 6h at ambient temperature. The reaction was quenched and worked-up in the usual fashion and examination of the reaction mixture showed the formation of a mixture of adduct (**69a**) as a single diastereoisiomer and sulphinyl acetate ($S_{(S)}$ R)-(-)-(**67**) (Scheme 63).



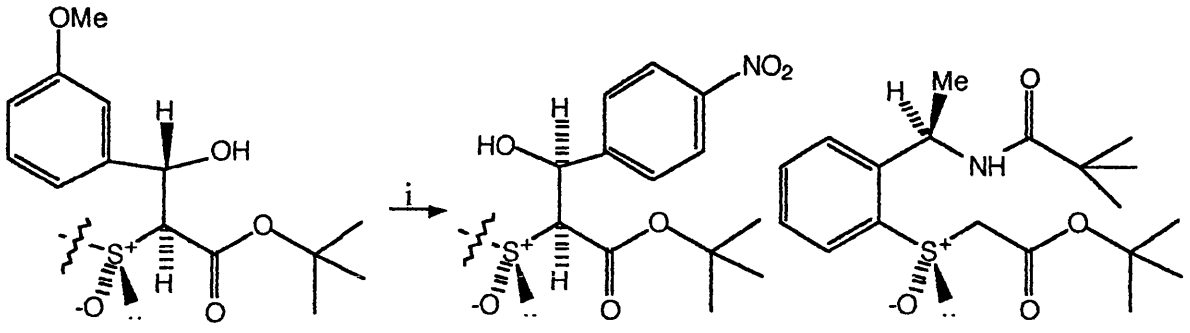
(**69c**) (**69a**) ($S_{(S)}$ R)-(-)-(**67**)

58% 20%

i *tert*-Butyl magnesium bromide, followed by benzaldehyde, -78°C for 6h, 6h at ambient temperature.

Scheme 63

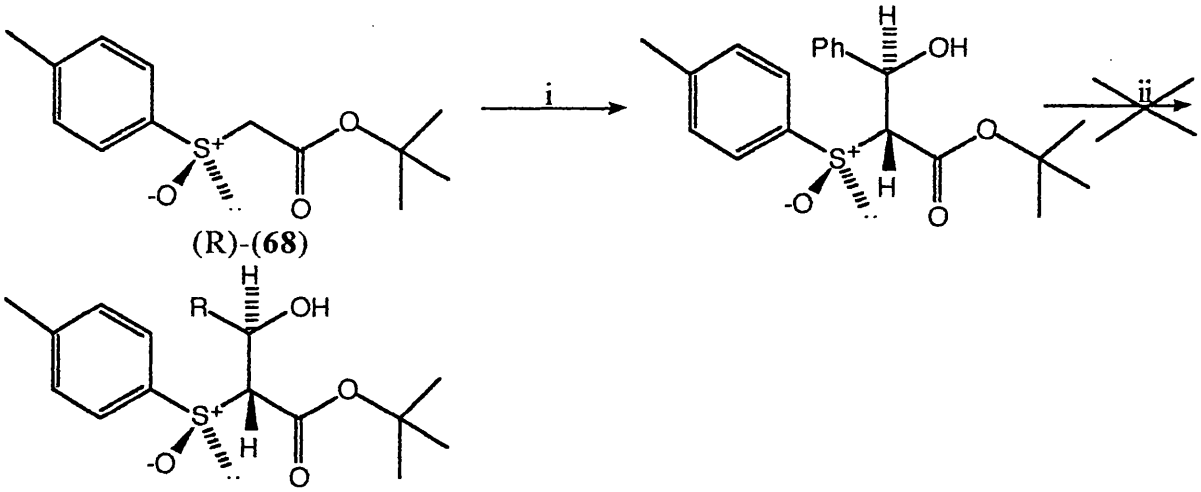
The above experiment was repeated with 4-nitrobenzaldehyde replacing benzaldehyde with the analogous result (Scheme 64).



i As in scheme 63, with 4-nitrobenzaldehyde replacing benzaldehyde,.

Scheme 64

The above experiments suggested that the major aldol product was formed *via* a thermodynamic equilibrium pathway with this process taking place at ambient temperature. The result appeared to be in conflict with those achieved with sulphinyl acetate (R)-(**68**) reported in the literature.[29] Experiments undertaken to check the related results showed that the low temperature quenching of the reaction between (R)-(**68**) and benzaldehyde had no effect on the high selectivities observed (Scheme 65).



i *tert*-Butyl magnesium bromide, followed by benzaldehyde, -78°C for 6h; or-78°C for 6h followed by 6h at ambient temperature, ii *tert*-Butyl magnesium bromide, followed by 4-methoxybenzaldehyde, -78°C for 6h; or -78°C for 8h followed by 6h at ambient temperature.

Scheme 65

A possible explanation for the observed equilibrium could be that the deprotonated amide side-chain was weakening the reactive metal complex through binding of the oxyanion. This would reduce the strength of binding of the aldehyde to the deprotonated enolate complex, and promote the reversibility of the reaction, generating the observed thermodynamic control.

From the results in table 12 the poor selectivity observed in the case of 2-methoxybenzaldehyde could not be due to steric considerations since the result obtained with the 2-nitrobenzaldehyde parallels that achieved with the unsubstituted benzaldehyde. The reason for the poor selectivity exhibited by 2-methoxybenzaldehyde must be electronic in nature. There are two possible explanations for this result;

a) The carbonyl group in 2-methoxybenzaldehyde would be electron rich due to the presence of the electron donating 2-methoxy-substituent. The electron rich carbonyl would bind more tightly to the magnesium in the transition state and such binding could prevent the thermodynamic equilibrium generating a kinetic result.

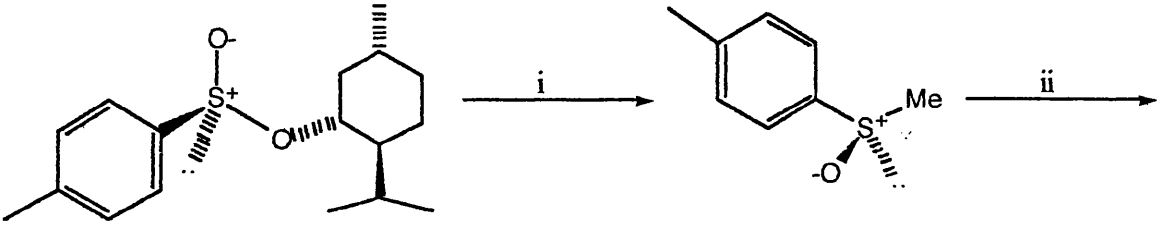
b) Or more likely the result could also be explained by proposing that the methoxy oxygen competed for the carbonyl coordination site on the magnesium. If such competition occurred the required transition state required for high selectivity could not form, causing a lowering of selectivity observed with 2-methoxybenzaldehyde.

2.3 Synthesis of β-Ketosulphoxides.

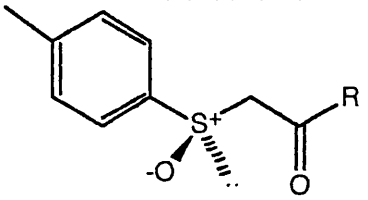
2.3.1 Previous synthesis of β-ketosulphoxides.

The synthesis of acyclic β-ketosulphoxides derived from (S)-(-)-(**25**) were based upon a two step procedure which involved initial reaction of (S)-(-)-(**25**) with methyl magnesium bromide to generate (R)-(+)-p-tolyl methyl sulphoxide (**74**).[91] Deprotonation of the methyl group with a strong base and the subsequent reaction of

the anion with an activated acid (usually an ester) generated the required β-ketosulphoxide (**75**) (Scheme 66).



(S)-(-)-(**25**) (R)-(+)-(**74**)

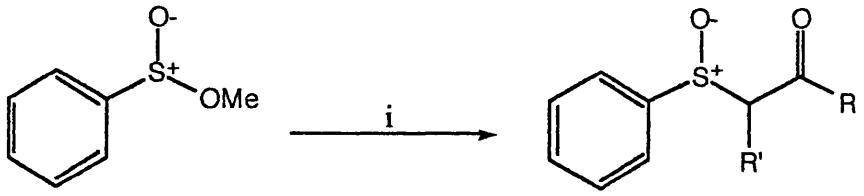


(R)-(**75**)

i Methyl magnesium bromide, diethyl ether, -78°C, ii Lithium diisopropylamide, RCOOEt, tetrahydrofuran, -78°C.

Scheme 66

In a related approach treatment of a ketone with sodium hydride (1.1 equivalents)[92], and subsequent reaction of the enolate with racemic methyl benzenesulphinate (**76**) generated the required β-ketosulphoxide (**77**) in good yield (Scheme 67).



(**76**) (**77**)

i Sodium hydride, ketone, tetrahydrofuran, ambient temperature.

Scheme 67

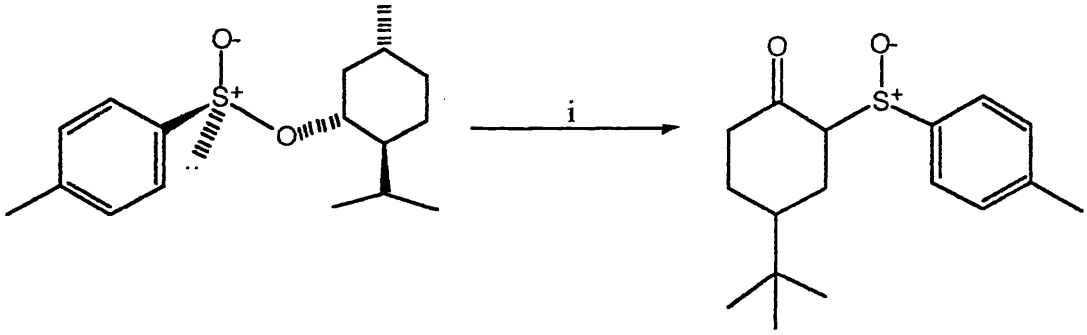
This approach has been applied to a variety of acyclic and cyclic ketones (table 16). Attempts to repeat this reaction with enantiomerically pure (**76**) resulted in the formation of products (**77**) of low enantiomeric purity.

Ketone	Yield %
3-Pentanone	65
Acetophenone	70
Cyclohexanone	74
Cyclooctanone	83
α-Tetralone	60
Camphor	50

Reaction of ketones with methyl benzenesulphinate (76)

Table 16

In an investigative study Wills and co-workers[93] found that treatment of the sodium enolate of 4-*tert*-butylcyclohexanone and (S)-(-)-(**25**) resulted in the formation of a racemic diastereomerically enriched (6:1) product (**78**) (Scheme 68).



(S)-(-)-(**25**) (**78**)

Racemic, diastereoisomerically enriched

i Sodium bis-(trimethylsilyl)amide, 4-*tert*-butylcyclohexanone, tetrahydrofuran, 0 °C.

Scheme 68

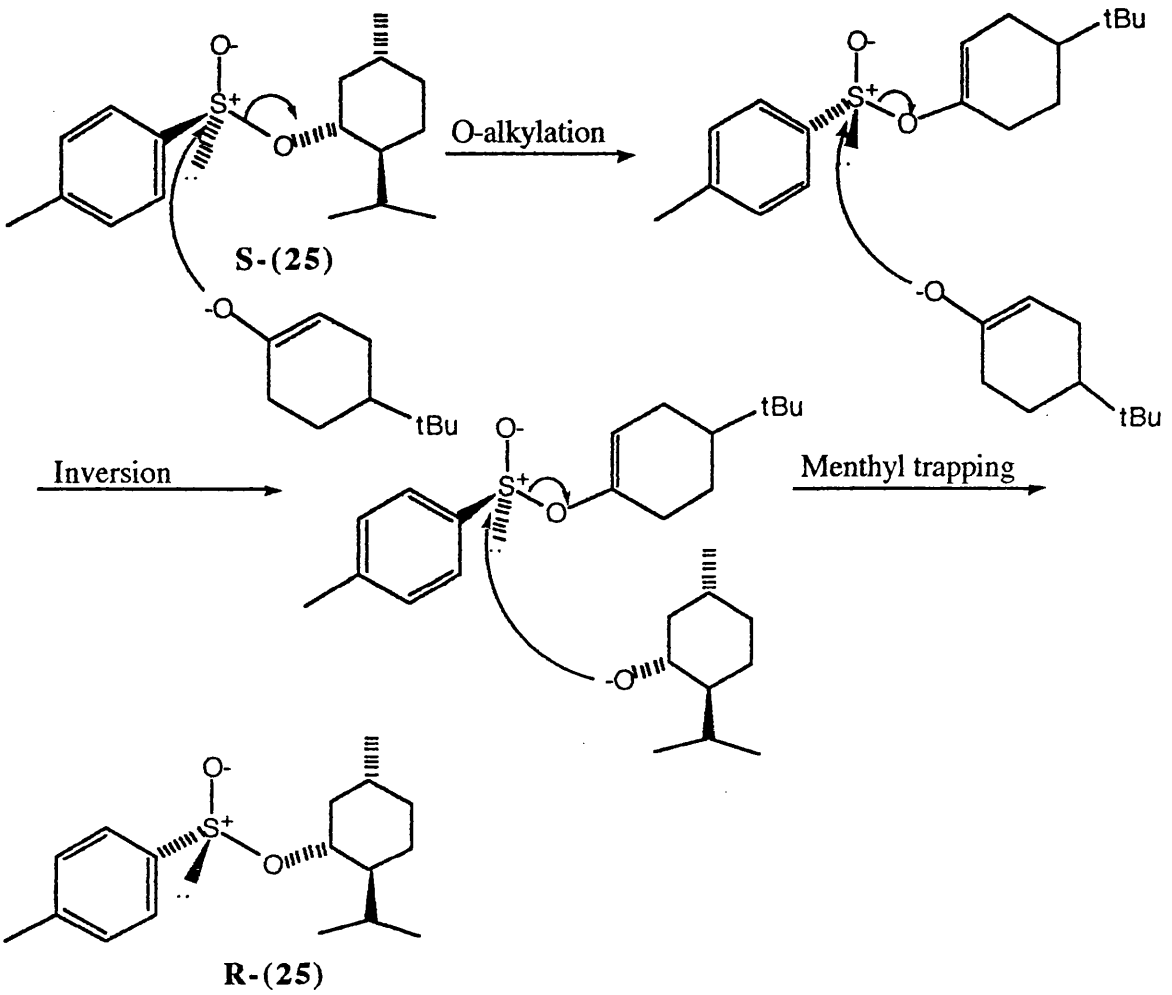
Two explanations may be proposed to rationalize the above racemisation results;

a) The sulphinate esters (S)-(-)-(**25**) and (**76**) had epimerised in the reaction, or

b) The resultant β-ketosulphoxide product had epimerised at the sulphoxide stereocentre after formation.

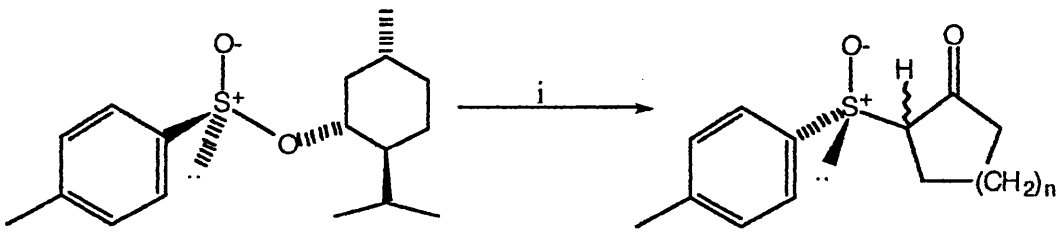
Literature evidence suggested that the latter rationale was unlikely, since no precedent existed to support such a base promoted epimerisation and it would be unlikely in view of the diastereoisomeric excess observed. In an attempt to examine if (S)-(-)-(**25**) was epimerised under the reaction conditions a sample of optically pure (S)-(-)-(**25**) was treated with *ca.* 0.3 equivalents of sodium menthoxide and the mixture stirred at ambient temperature for 24h. Thin layer chromatography examination of the reaction mixture showed that no (R)-(**25**) was present. A quantity of 4-*tert*-butylcyclohexanone (0.2 equivalents) was added and the reaction monitored by thin layer chromatography. After 0.5h, as well as showing a quantity of (**78**), (R)-(**25**) was observed.

The conclusion drawn from this experiment was that the ketone enolate was responsible for the epimerisation of (S)-(-)-(**25**). The epimerisation was probably *via* O-alkylation by the ketone enolate followed by sulphinyl exchange between enolates *via* an S_N2 pathway, hence resulting in the formation of racemic (25) (Scheme 69). Racemic (**25**) could react with the carbon nucleophile generating the observed racemic (**78**).



Scheme 69

Carreno and co-workers[94] have reported that treatment of cyclic ketones with magnesium bromide diisopropylamide in benzene followed by the addition of enantiomerically pure (S)-(**25**) resulted in the formation of adducts (**79**) (Scheme 70 and table 17). Adducts (**79**) were found to be single stereoisomers at the sulphoxide stereocentre, but epimeric at the C-2 centre. Recrystallisation of the diastereoisomeric mixtures generated optically pure adducts (**79**).



n=1,2 or 3

(S)-(**25**) (**79**)

i Magnesium bromide diisopropylamide, ketone, benzene, 0°C.

Scheme 70

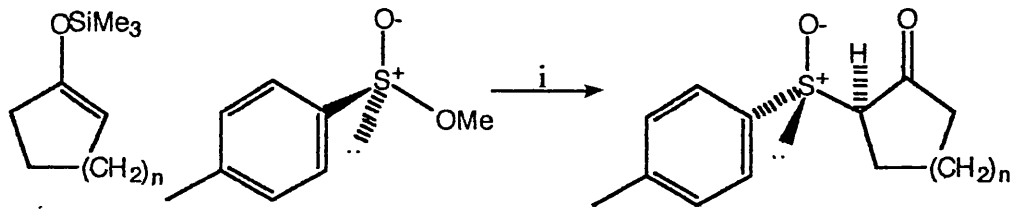
Cycloalkanone	Yield[a] %
Cyclopentanone	24
Cyclohexanone	70
Cycloheptanone	83

a Of the C-2 diasteroisomeric mixtures.

Cyclic β-ketosulphoxides derived from the reaction between the magnesium bromide enolate and (S)-(-)-(25)

Table 17

It had been reported[95] that the reaction of silyl enol ethers of cyclic ketones (**80**) with methyl (S)-p-tolylsulphinate (**81**) in the presence of a Lewis acid proceeded to give β-ketosulphoxides (**79**) with high selectivity (Scheme 71 and table 18).



n=1,2 or 3

(**80**) (S)-(**81**) (**79**)

i Lewis acid (see table), dichloromethane.

Scheme 71

n	Lewis acid	Yield of (79) %	Specificity[a] of (81) to (79) %
1	BF_3-OEt_2	90	85.7
1	$TiCl_4$	26	63.2
1	$SnCl_4$	58	54.6
2	BF_3-OEt_2	95	98.3
2	$TiCl_4$	42	74.9
2	$SnCl_4$	40	80.0
3	BF_3-OEt_2	93	90.5
3	$TiCl_4$	39	71.9
3	$SnCl_4$	22	59.4

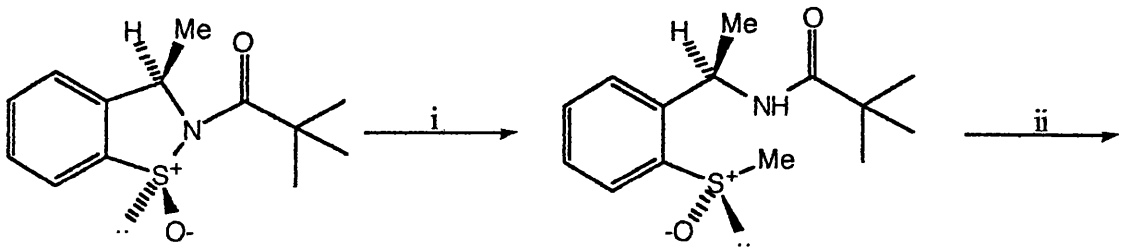
a. Only enantiomerically enriched (**81**) used, not enantiomerically pure

Reaction of silyl enol ethers (80) with enantiomerically enriched (81).

Table 18

2.3.2. Synthesis of β-ketosulphoxides derived from cyclic sulphinamide (**59**).

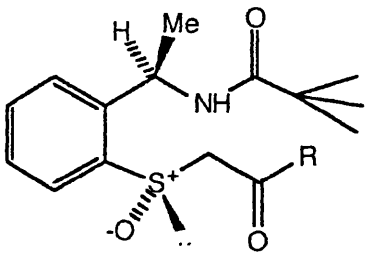
The initial synthesis of β-ketosulphoxides derived from ($S_{(S)}$ R)-(+)-*cis*-(**59**) used the same synthetic strategy utilized for (S)-(**25**) derived β-ketosulphoxides. Reaction of ($S_{(S)}$ R)-(+)-*cis*-(**59**) with methyl magnesium bromide generated the required crystalline ($S_{(S)}$ R)-(-)-methyl sulphoxide (**82**) in 84% yield. Addition of a solution of ($S_{(S)}$ R)-(-)-(**82**) to a tetrahydrofuran solution of lithium diisopropylamine (5 equivalents) generated the anion, which upon reaction with ethyl benzoate gave β-ketosulphoxide ($S_{(S)}$ R)-(-)-(**83**) as a crystalline solid in 94% yield (Scheme 72).



($S_{(S)}$ R)-(+)-*cis*-(**59**)

($S_{(S)}$ R)-(-)-(**82**)

84%



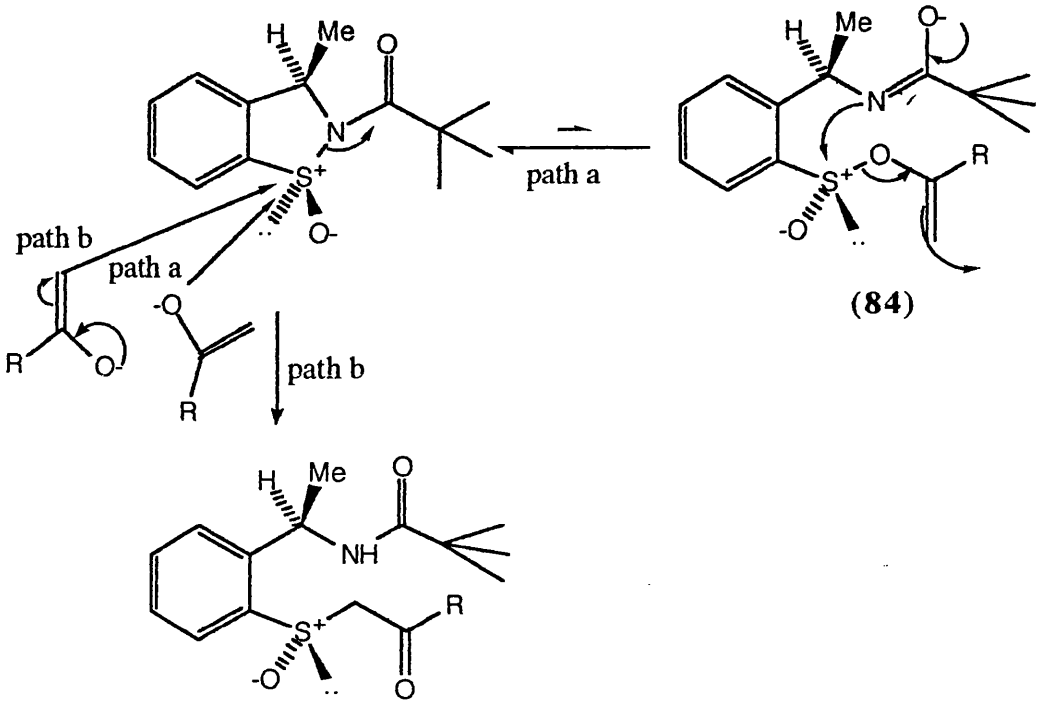
($S_{(S)}$ R)-(-)-(**83**)

94%

i Methyl magnesium bromide, diethyl ether, -78°C, ii Lithium diisopropylamide (5 equivalents), ($S_{(S)}$ R)-(-)-(**82**), RCOOEt, 0°C.

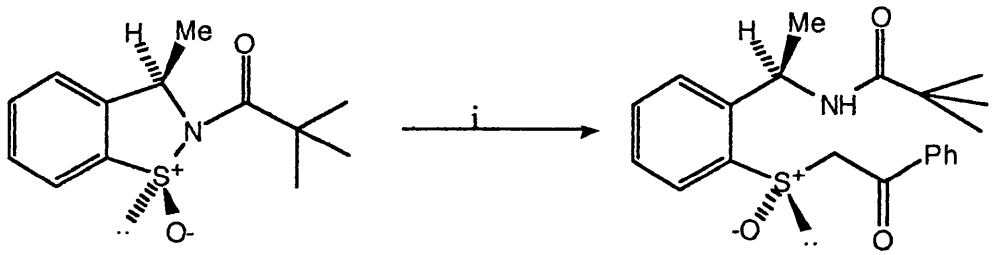
Scheme 72

However, a simpler one step procedure was sought. From the proposed rationale for the epimerisation of (S)-(**25**) described by Wills and co-workers[93] it was thought that the reaction of a ketone enolate with (**59**) would result in the formation of β-ketosulphoxides with high stereochemical purity. If the enolate reacted through oxygen (path a), effecting ring opening to generate intermediate (**84**), subsequent ring closure with expulsion of the enolate would occur at a faster rate than any intermolecular reaction, hence preventing racemization. Thus reaction *via* the carbon nucleophile (path b) would result in irreversible ring opening, proceeding with overall inversion of configuration at sulphur (Scheme 73).



Scheme 73

Acetophenone was deprotonated by a variety of bases in different solvents in an attempt to probe this possible novel methodology (Scheme 74 and table 19). Addition of a solution of the ketone (1 equivalent in a 1M solution in the solvent) to the pre-formed base (1 equivalent, 1.0M in THF) at -78°C in the required solvent followed by stirring at this temperature for 1h allowed for deprotonation. Addition of a solution of ($S_{(S)}$ R)-(+)-*cis*-(**59**) (0.4 equivalents, 0.4M in the named solvent) at -78°C and stirring at this temperature for 1h followed by 1h at ambient temperature resulted in formation of the required β-ketosulphoxide. The crude β-ketosulphoxide was purified by column chromatography and analyzed by ^{1}H NMR spectroscopy.



($S_{(S)}$ R)-(+)-*cis*-(**59**) ($S_{(S)}$ R)-(-)-(**85**)

i Base (see table), acetophenone, solvent, -78°C to ambient temperature.

Scheme 74

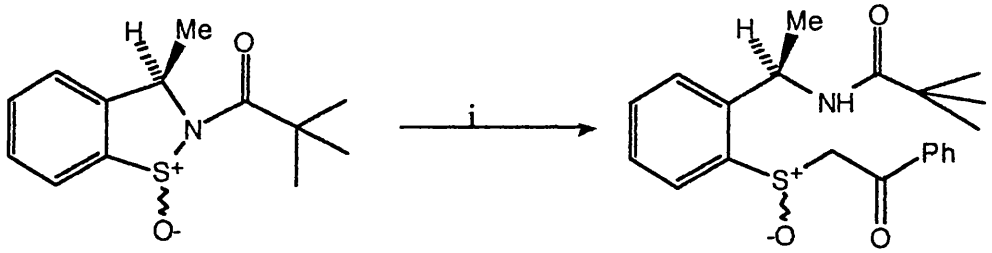
Base/Solvent	Tetrahydrofuran	Diethyl ether	Toluene
LDA	13%	35%	35%
MgBrDA	14%	<5%	<5%
NaHMDS	19%	47%	71%

LDA - lithium diisopropylamide, MgBrDA - magnesium bromide diisopropylamide, NaHMDS - Sodium bis-(trimethylsilyl)amide. The mass balance was accounted for by unreacted ($S_{(S)}$ R)-(+)-*cis*-(**59**).

Base/solvent dependancy in the conversion of ($S_{(S)}$ R)-(+)-*cis*-(59) to ($S_{(S)}$ R)-(-)-(85).

Table 19

All the above reactions gave ($S_{(S)}$ R)-(-)-(**85**) as a single diastereoisomer by examination of the ^1H NMR spectrum. To confirm there was no coincidence of proton resonance signals, a sample of epimeric (**59**) (3:2) was treated with the sodium enolate of acetophenone in toluene. Examination of the ^1H NMR spectrum revealed a well resolved set of signals corresponding to the proton resonances of each diastereoisomer. The diastereoisomeric mixture of (**85**) matched the ratio in the starting epimeric (**59**) (Scheme 75).



(59) **(85)**

3:2 3:2

i Sodium bis-(trimethylsilyl)amide, acetophenone, toluene, -78°C to ambient temperature.

Scheme 75

From table 19 it could be seen that the optimum conditions for the reaction between acetophenone and ($S_{(S)}$ R)-(+)-*cis*-(**59**) involved the use of the sodium enolate generated from sodium bis-(trimethylsilyl)amide in toluene. Attempts to replace sodium bis-(trimethylsilyl)amide with sodium hydride resulted in no reaction between ($S_{(S)}$ R)-(+)-*cis*-(**59**) and acetophenone.

The generality of formation of β-ketosulphoxides utilizing this methodology was subsequently probed A series of other mono-enolizable ketones (i.e. ketones which can generate the enolate in one direction) were deprotonated with sodium bis-(trimethyl)silylamide and the enolates subsequently reacted with ($S_{(S)}$ R)-(+)-*cis*-(**59**) (table 20).

Ketone	Yield %	β-Ketosulphoxide
4-Methoxyacetophenone	quantitative	($S_{(S)}$ R)-(-)-(**86**)
2-Methylacetophenone	73	($S_{(S)}$ R)-(-)-(**87**)
Pinacolone	70	($S_{(S)}$ R)-(-)-(**88**)
Propiophenone	75[a]	(**89**)

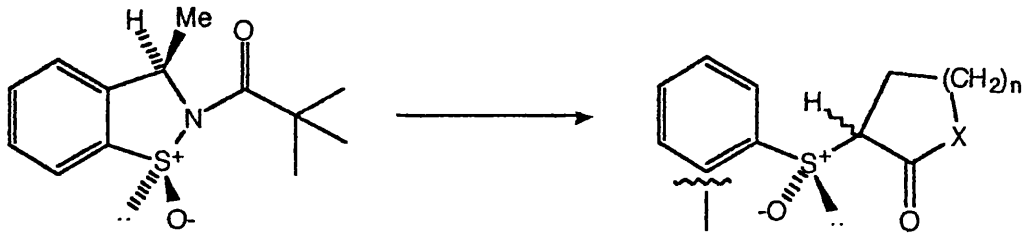
a Product (**89**) was isolated as a 3:2 mixture of diastereoisomers at C-2

Synthesis of β-ketosulphoxides derived from mono-enolizable ketones and ($S_{(S)}$ R)-(+)-*cis*-(59).

Table 20.

The results were very encouraging with a single crystalline diastereoisomer formed in all the examples, except (**89**). The lack of coincident proton resonances was proven by the synthesis of an epimeric mixture of each adduct from epimeric (**59**). Examination of the ^1H NMR spectrum showed distinct signals for the proton resonances for each epimer. From the above results it would appear that the more reactive the enolate, the higher the yield of β-ketosulphoxide (comparing the yields for ($S_{(S)}$ R)-(-)-(**85**) and ($S_{(S)}$ R)-(-)-(**86**)).

The nature of the ketone type examined was subsequently extended to cyclic ketones and a single example of a lactone (Scheme 76 and table 21).



($S_{(S)}$ R)-(+)-*cis*-(**59**)

i Sodium bis-(trimethylsilyl)amide, ketone, toluene, -78°C to ambient temperature.

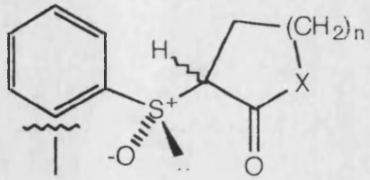
Scheme 76

n	X	Yield %	β-Ketosulphoxide
1	O	76	(**90**)
1	CH_2	45	(**91**)
2	"	78	(**92**)
3	"	98	(**93**)
6	"	88	(**94**)
11	"	76	(**95**)

Synthesis of cyclic β-ketosulphoxides from ($S_{(S)}$ R)-(+)-*cis*-(59)

Table 21

Upon examination of the ^1H NMR spectral data for the above reactions it was found that diastereoisomeric mixtures, epimeric at C-2, had been formed (table 22 and figure 10). β-Ketosulphoxide (**92**) derived from cyclohexanone was crystallised from dichloromethane and subjected to a single crystal X-ray determination. The structure determined (figure 11) showed that the required inversion of stereochemistry had taken place at the sulphur atom. Assuming the same reaction pathway had been followed in the synthesis of the other cyclic β-ketosulphoxides, the epimeric position will be at C-2 and not at sulphur.



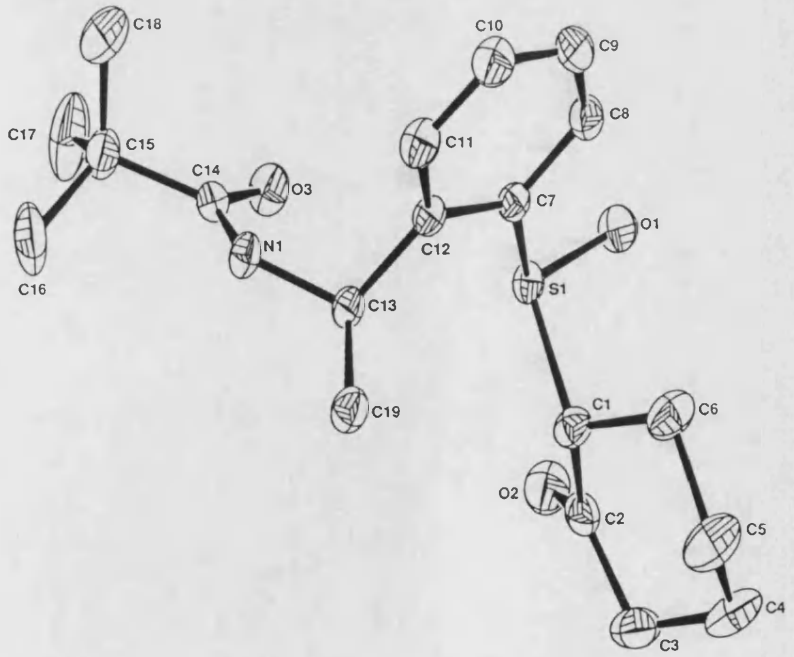
Showing the epimeric C-2 position.

Figure 10

β-Ketosulphoxide	Diastereoisomeric ratio at C-2
(90)	10:1
(91)	10:1
(92)	>25:1
(93)	1:1
(94)	1:1
(95)	1:1

Diastereoisomeric ratios for the cyclic β-ketosulphoxides

Table 22.



X-ray structure of diastereoisomerically pure cyclohexanone adduct (92).

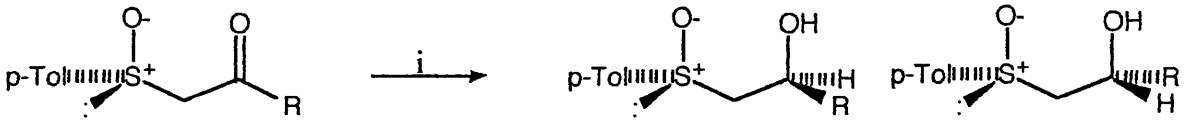
Figure 11

2.4. Reduction of the β-Ketosulphoxides.

2.4.1 Reduction of acyclic β-ketotosulphoxides

With the successful synthesis of the β-ketosulphoxides attention was turned towards the chemistry associated with these valuable intermediates.

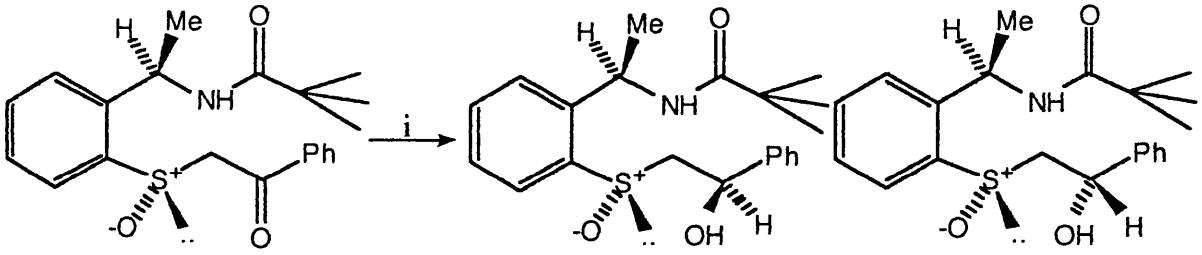
The diastereoselective reduction of β-ketosulphoxides to either epimeric β-hydroxysulphoxide with high stereospecificity, dependant upon the nature of the reducing agent, has been discussed (Scheme 77).[32, 33]



i Reducing agent.

Scheme 77

In seeking the specificity exhibited by β-ketosulphoxides derived from ($S_{(S)}$ R)-(+)-*cis*-(**59**) reduction of ($S_{(S)}$ R)-(-)-(**85**) was investigated using a variety of reducing agents (Scheme 78 and table 23) to generate mixtures of β-hydroxysulphoxides ($S_{(S)}$ R, S)-(-)-(**96**) and ($S_{(S)}$ R, R)-(-)-(**97**).



($S_{(S)}$ R)-(-)-(**85**) ($S_{(S)}$ R, S)-(-)-(**96**) ($S_{(S)}$ R, R)-(-)-(**97**)

i Reducing agent (see table).

Scheme 78

All reactions were carried out on a 0.27mmol scale in anhydrous tetrahydrofuran at -78°C, except the sodium borohydride cerium (III) chloride reaction which was carried

out in methanol at ambient temperature. The selectivity was assessed by utilizing ^1H NMR spectroscopy.

Reducing agent	Yield %	($S_{(S)}$ R, S)-(-)-(96)	($S_{(S)}$ R, R)-(-)-(97)
DIBAL-H	73	94	6
NBu_4BH_4	quantitative	62	38
$NaBH_4$	"	60	40
$NaBH_4/CeCl_3$	"	57	43
$NaB(OAc)_3H$	"	40	60
$LiAlH_4$	87	25	75
DIBAL-H /$ZnBr_2$	80	<2	>98

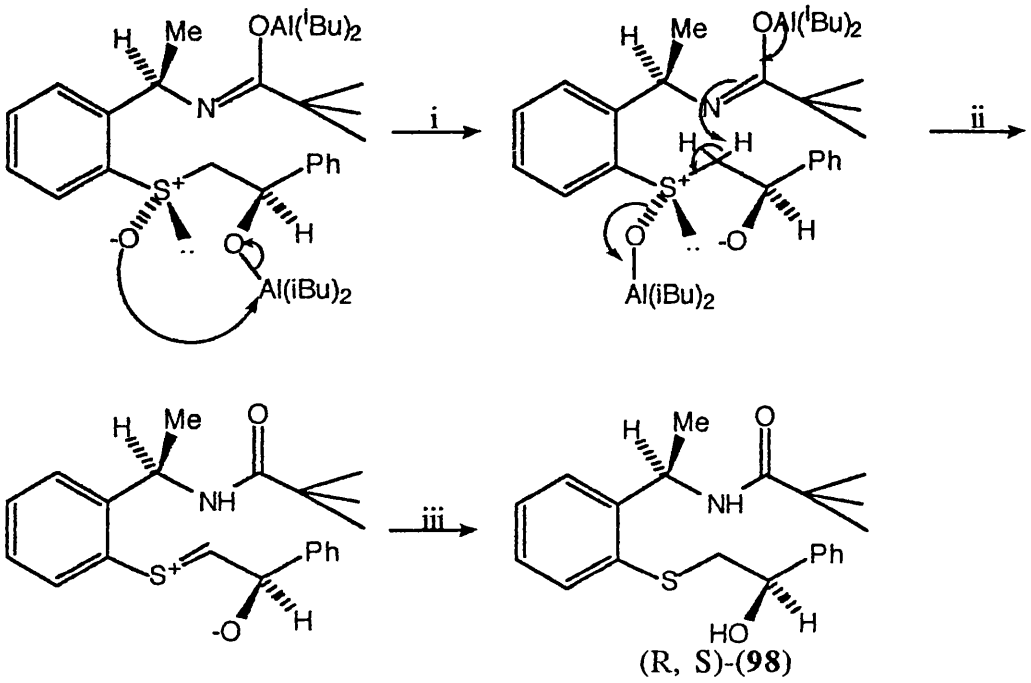
Reduction of β-ketosulphoxide ($S_{(S)}$ R)-(-)-(85)

Table 23

In the cases of low diastereoisomeric excess, the signal corresponding to the aromatic proton adjacent to the sulphoxide in each diastereoisomer was distinct. Integration of this resonance furnished the required ratios whereas in examples of high diastereoisomeric excess examination of the proton signals from the methylene group provided the required ratio. This method could not be used upon mixtures with low ratios due to the complexity of the two approximately equal methylene ratios. The arbitrary assignment of quantitative equates to full mass recovery of products pure by ^1H NMR spectroscopy. Assignment of the products was based upon comparison of the relative ^1H NMR spectroscopic data from previous work in the literature.[32, 33]

As a by-product (*ca* 10%) the hydroxysulphide (R, S)-(**98**) (as assessed from the ^1H NMR spectroscopic data) was observed in the DIBAL-H reduction of ($S_{(S)}$ R)-(-)-(**85**). The product (R, S)-(**98**) may arise from an aluminium Pummerer-type reaction of the hydroxysulphoxide ($S_{(S)}$ R, S)-(-)-(**96**), since the diastereoisomeric ratio

observed in compound (R, S)-(**98**) matched that observed with ($S_{(S)}$ R, S)-(-)-(**96**). A possible mechanism for the process is shown in figure 12.



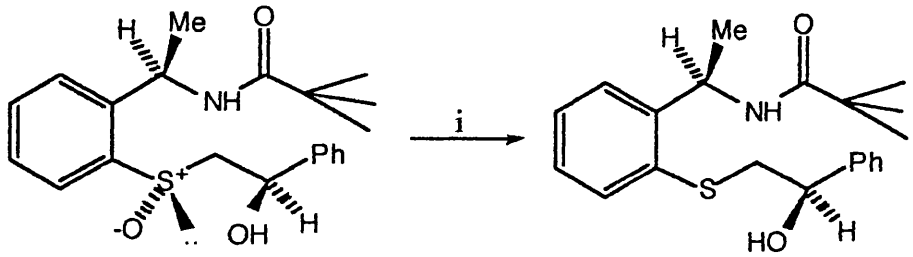
(R, S)-(**98**)

i Transfer of aluminium residue from hydroxyl to sulphoxide, ii Pummerer reaction utilizing the internal amide as base, iii Reduction of sulphonium species.

Formation of the β-hydroxysulphide (R, S)-(98) from the corresponding β-hydroxysulphoxide ($S_{(S)}$ R, S)-(-)-(96).

Figure 12

An authentic sample of (R, S)-(**98**) was synthesised in 64% by reduction of ($S_{(S)}$ R, S)-(-)-(**96**) utilizing the triphenylphosphine-iodine protocol (Scheme 79).



($S_{(S)}$ R, S)-(-)-(**96**) (R, S)-(**98**)

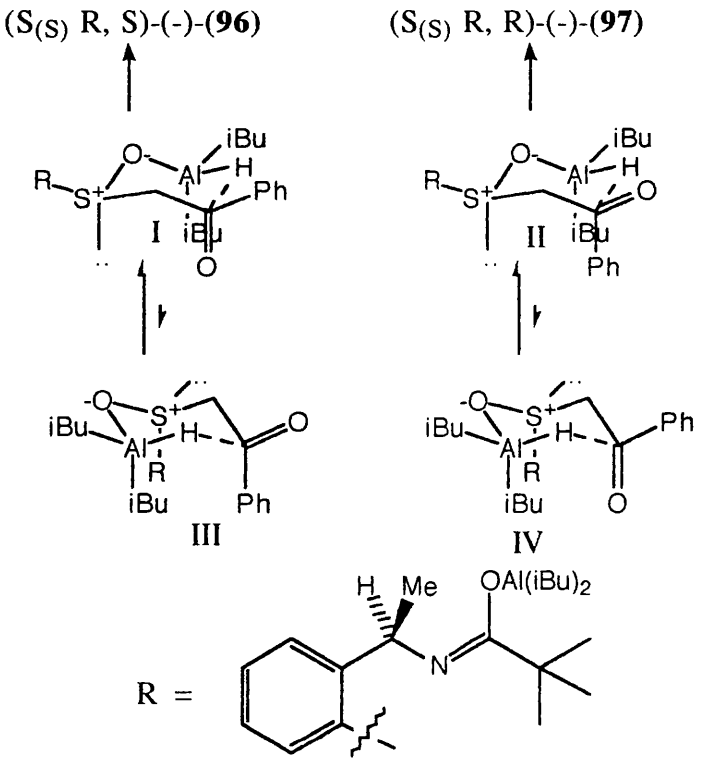
64%

i Triphenylphosphine, iodine, acetonitrile, ambient temperature.

Scheme 79

2.4.2 Reasons for selectivity observed.

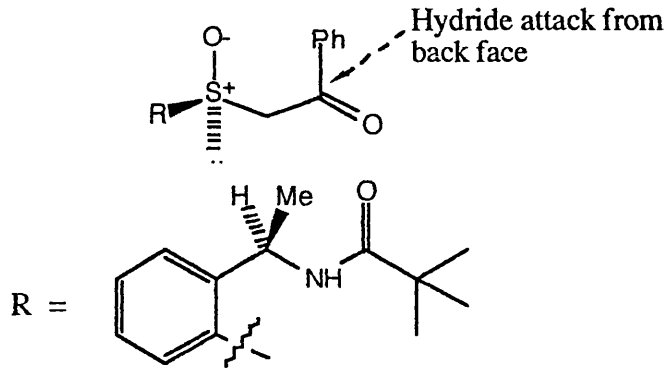
The selectivity exhibited by DIBAL-H in generating ($S_{(S)}$ R, S)-(-)-(**96**) in 88% diastereoisomeric excess could be explained by the transition state shown in figure 13. The Lewis acidic aluminium formed an Al-O bond with the basic sulphinyl oxygen and from this adduct the intramolecular hydride transfer would take place through a chair-type transition state. Four different transition states can be postulated. The 1,3-diaxial interaction present in III and IV makes them unfavourable. Reduction through I and II would result in the formation of different products, I would give rise to the required *trans*- product ($S_{(S)}$ R, S)-(-)-(**96**). The increased stability of I (no 1,3-diaxial interaction) would explain the predominance of ($S_{(S)}$ R, S)-(-)-(**96**) in the reaction mixture.



The possible transition states leading to the observed *trans* : *cis* ratio in the reduction of ($S_{(S)}$ R)-(-)-(85).

Figure 13

The low selectivities observed in the case of the borohyride reducing agents could be rationalised by invoking a "loose" transition state (figure 14). Ketone (**85**) orientated in such a fashion to minimize dipole-dipole interactions would adopt the conformation as shown. Hydride attack would then occur from the less hindered face of the carbonyl favouring the major product ($S_{(S)}$ R, S)-(-)-(**96**) as observed.



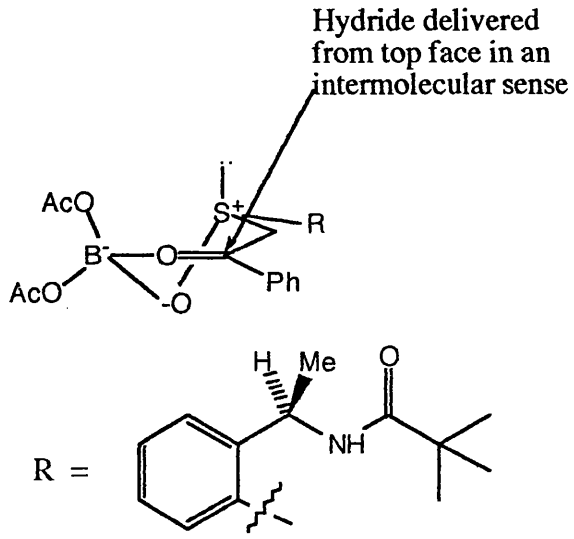
The loose transition state for the borohydride reduction.

Figure 14

Since in this transition state there can be no constraint present, free rotation about the carbon-carbon bond could occur, leading to the generation of diastereoisomer ($S_{(S)}$ R, R)-(-)-(**97**).

Sodium triacetoxyborohydride[96] was introduced as a chelating reducing agent for β-hydroxyketones generating *trans*-1,3-diols with high degrees of stereoselectivity. The observed opposite selectivity (generation of ($S_{(S)}$ R, R)-(-)-(**97**) as the major product) may be reasoned by the formation of a chelated species which would then undergo intermolecular hydride addition from the top face of the carbonyl (Figure 15).

Since the observed selectivity was low (20% d.e.) the chelate formed must be weak allowing reduction to also occur through an unchelated species.

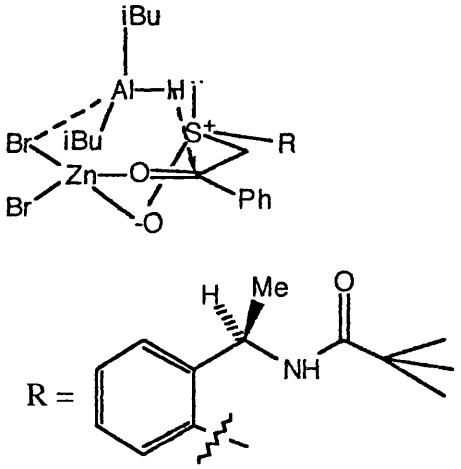


Weakly coordinated transition state for sodium triacetoxyborohydride.

Figure 15

The higher selectivity for the formation of ($S_{(S)}$ R, R)-(-)-(**97**) observed with lithium aluminium hydride could be rationalised by the greater coordinating ability of the lithium counter-ion, thus the same transition state as proposed for sodium triacetoxyborohydride can be invoked.

The utilization of the zinc (II) bromide-DIBAL-H protocol resulted in the highest selectivity observed for ($S_{(S)}$ R, R)-(-)-(**97**). The selectivity observed for ($S_{(S)}$ R, R)-(-)-(**97**) was in accordance with the published data for the reduction of acetophenone derived β-ketosulphoxides. The transition state illustrated in figure 16 would explain the high selectivity achieved. The zinc (II) bromide acted as a chelating species, generating a very tight thermodynamically favourable chelate. Subsequently the bromide atom in the *psuedo-axial* position[34] bound to the aluminium of the DIBAL-H forming a bridged, bimetallic species. The DIBAL-H was then in the correct orientation to affect delivery of the hydride to the carbonyl, generating ($S_{(S)}$ R, R)-(-)-(**97**) with high selectivity.

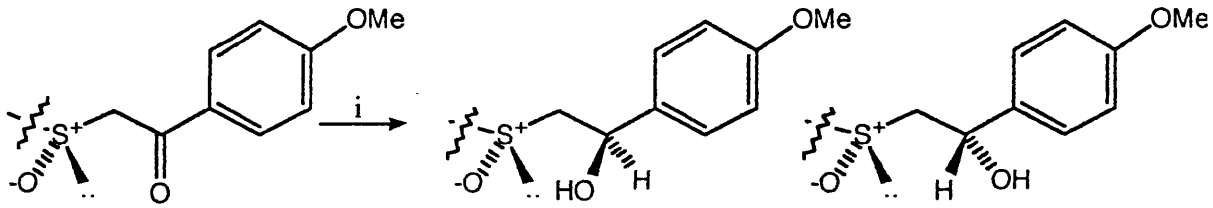


Transition state proposed to rationalise the DIBAL-H zinc (II) bromide selectivity.

Figure 16

2.4.3 Extention of reduction protocol to other acyclic β-ketosulphoxides.

The two complementary reduction protocols, DIBAL-H and DIBAL-H zinc (II) bromide, were then applied to the other C-2 unsubstituted aromatic β-ketosulphoxides (Scheme 80 and 81, table 24 and 25)



($S_{(S)}$ R)-(-)-(**86**) ($S_{(S)}$ R, S)-(-)-(**99**) ($S_{(S)}$ R, R)-(-)-(**100**)

i Reducing agent, tetrahydrofuran, -78°C.

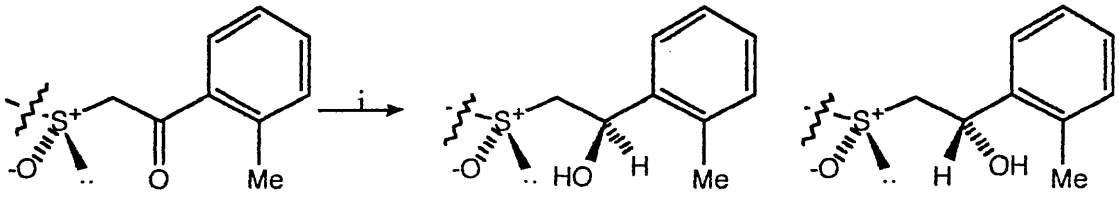
Scheme 80

Reducing agent	Yield %	($S_{(S)}$ R, S)-(-)-(99)	($S_{(S)}$ R, R)-(-)-(100)
DIBAL-H	90[a]	91	9
DIBAL-H /$ZnBr_2$	100[b]	<2	>98

a. Remaining 10% unreacted starting material. b. Full mass recovery.

Reduction of β-ketosulphoxide ($S_{(S)}$ R)-(-)-(86)

Table 24



($S_{(S)}$ R)-(-)-(**87**) ($S_{(S)}$ R, S)-(-)-(**101**) ($S_{(S)}$ R, R)-(-)-(**102**)

i Reducing agent, tetrahydrofuran, -78°C.

Scheme 81

Reducing agent	Yield %	($S_{(S)}$ R, S)-(-)-(101)	($S_{(S)}$ R, R)-(-)-(102)
DIBAL-H	90[a]	91	9
DIBAL-H /$ZnBr_2$	90	<2	>98

a. Remaining 10% unreacted starting material.

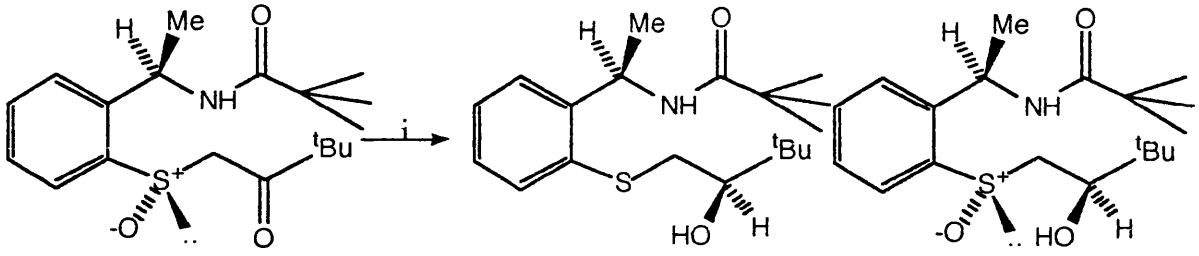
Reduction of β-ketosulphoxide ($S_{(S)}$ R)-(-)-(87)

Table 25

The results from the two protocols were encouraging with high selectivity displayed by the DIBAL-H zinc (II) bromide methodology. In the cases of ($S_{(S)}$ R)-(-)-(**86**) and ($S_{(S)}$ R)-(-)-(**87**) DIBAL-H reduction had not resulted in the over reduction to the corresponding β-hydroxysulphide.

Reduction of the pinacolone derived β-ketosulphoxide ($S_{(S)}$ R)-(-)-(**88**) with DIBAL-H resulted in the isolation of β-hydroxysulphide (R, S)-(-)-(**103**) in 55% chemical

yield and 88% diastereoisomeric excess. The corresponding β-hydroxysulphoxide ($S_{(S)}$ R, S)-(-)-(**104**) was isolated in 10% chemical yield with the same diastereoisomeric excess (Scheme 82).



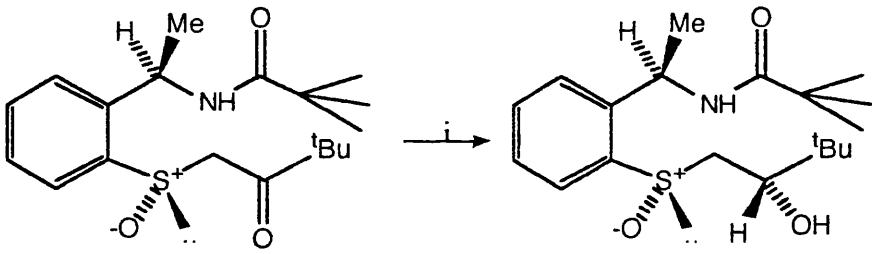
($S_{(S)}$ R)-(-)-(**88**) (R, S)-(-)-(**103**) ($S_{(S)}$ R, S)-(-)-(**104**)

55% 10%

i DIBAL-H , tetrahydrofuran, -78°C.

Scheme 82

The converse reaction with DIBAL-H zinc (II) bromide proceeded in the standard fashion (Scheme 83) to give ($S_{(S)}$ R, R)-(-)-(**105**) in 90% yield with greater than 96% d.e. The resultant mass balance was accounted for by unreduced ($S_{(S)}$ R)-(-)-(**88**).



($S_{(S)}$ R)-(-)-(**88**) ($S_{(S)}$ R, R)-(-)-(**105**)

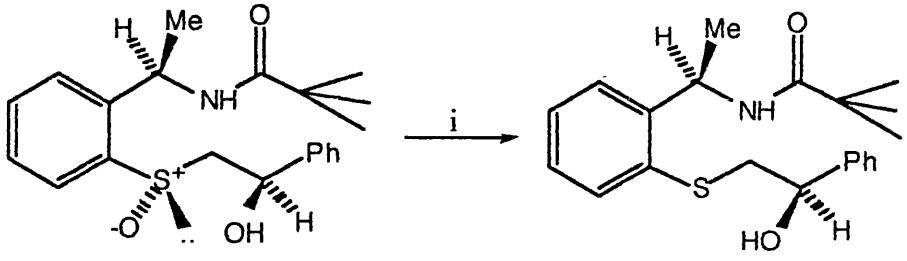
90%

i DIBAL-H, zinc (II) bromide, tetrahydrofuran, -78°C.

Scheme 83

The over-reduction of β-ketosulphoxides to the corresponding β-hydroxysulphide appeared to be the major pathway for non-aromatic β-ketosulphoxides, but a minor route in the case of unsubstituted aromatic β-ketosulphoxides. That this phenomenon occurred after reduction of the ketone was subsequently investigated. Treatment of β-hydroxysulphoxide ($S_{(S)}$ R, S)-(-)-(**96**) with DIBAL-H (4 equivalents) in

tetrahydrofuran at -78°C for 2h resulted in the formation of (R, S)-(**98**) in 30% yield. The resulting mass balance was accounted for by unreacted ($S_{(S)}$ R, S)-(-)-(**96**) (Scheme 84). Extended reaction time, increased amounts of reducing agent or elavated temperatures failed to increase the yield of (R, S)-(**98**).



($S_{(S)}$ R, S)-(-)-(**96**) (R, S)-(**98**)

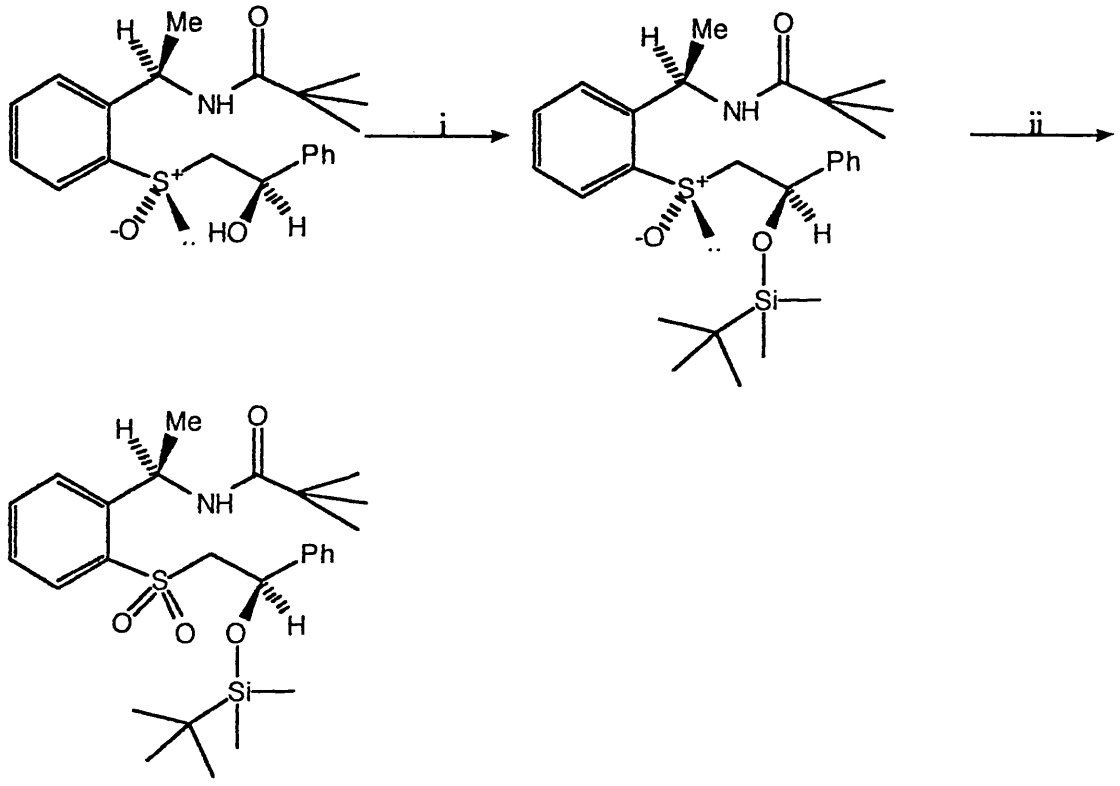
30%

i DIBAL-H (4 equivalents), tetrahydrofuran, -78°C.

Scheme 84

2.4.4 Attempted removal of the sulphinyl unit from the β-hydroxysulphoxides.

Protection of the β-hydroxysulphoxide ($S_{(S)}$ R, S)-(-)-(**96**) as the *tert*-butyldimethylsilyl ether[97] followed by oxidation of the sulphoxide with sodium periodate in the presence of a catalytic amount of ruthenium (III) chloride[98] resulted in the formation of the sulphone (R, S)-(**106**) in 58% chemical yield from ($S_{(S)}$ R, S)-(-)-(**96**) (Scheme 85).



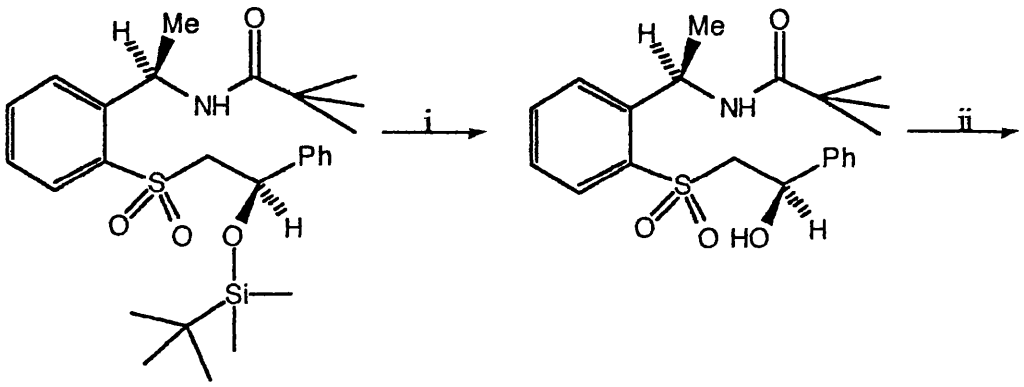
(R, S)-(**106**)

58% for two steps

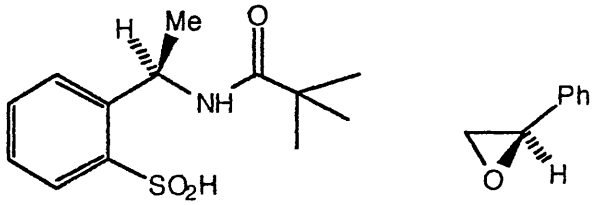
i *tert*-Butyldimethylsilyl chloride, imidazole, DMF, ii Sodium periodate, ruthenium (III) chloride, carbon tetrachloride, acetonitrile, water.

Scheme 85

It was proposed that upon deprotection of the hydroxy group alcohol (R, S)-(**107**) would be deprotonated resulting in the displacement of the sulphone generating sulphinic acid (R)-(-)-(**61**) and homochiral styrene oxide (S)-(**108**) (Scheme 86). Sulphinic acid (R)-(-)-(**61**) could then be cyclized to give ($S_{(S)}$ R)-(+)-*cis*-(**59**) fulfilling the role of ($S_{(S)}$ R)-(+)-*cis*-(**59**) as a recyclable source of homochiral sulphoxide.



(R, S)-(**106**) (R, S)-(**107**)

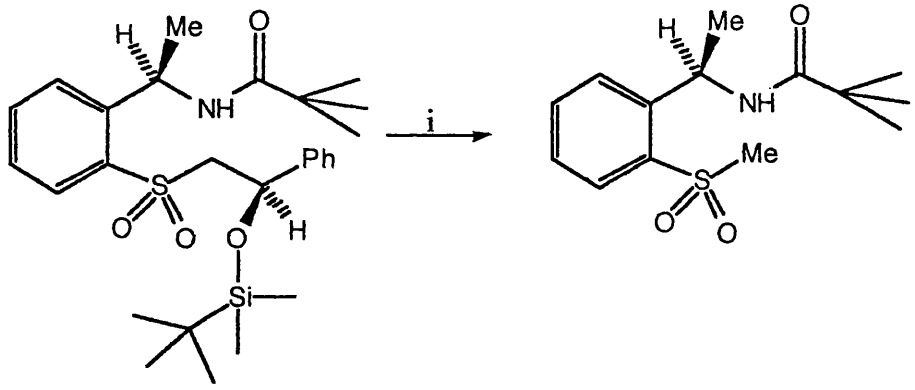


(R)-(-)-(**61**) (S)-(**108**)

i Removal of the silyl ether, ii Deprotonation of alcohol.

Scheme 86

Treatment of (R, S)-(**106**) with tetrabutylammonium fluoride (TBAF)[97], (**106**) caused a retro-aldol reaction to generate methyl sulphone (R)-(**109**) in 89% yield (Scheme 87).



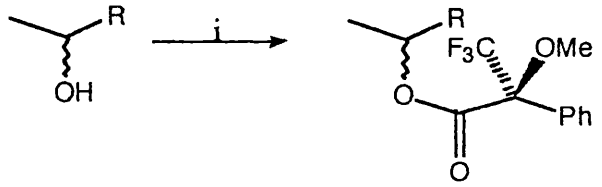
(R, S)-(**106**) (R)-(**109**)

89%

i TBAF, tetrahydrofuran.

Scheme 87

With the failure of this approach and the instability of the amide side-chain under Pummerer[18] conditions, Raney™ nickel[16] methodology was investigated. Before this methodology was studied a means for assessing the enantiomeric excess of the cleaved alcohols had to be developed. Chiral shift experiments with **(72)** proved inadequate hence the alcohols were converted to the corresponding Mosher[99] ester derivatives. A sample of racemic alcohol (commercially available or *via* the sodium borohydride reduction of the ketone) was treated with (R)-(+)-methoxytrifluoromethylphenyl acetic acid ((R)-(+)-MTPA) in the presence of dicyclohexylcarbodiimide (DCC)[100] to generate the diastereoisomeric mixture of Mosher esters (Scheme 88 and table 26).



i R-(+)-MTPA, DCC, 4-dimethylaminopyridine,chloroform, ambient temperature, 16h.

Scheme 88

Alcohol	Methyl	Methoxy	Methyne	Other
3,3-dimethylbutan-2-ol	1.19 and 1.29	3.51 and 3.56	4.85 and 4.90	0.87 and 0.90[a]
1-methyl-(2-methylbenzene) methanol	1.45 and 1.52	3.41 and 3.50	6.19 and 6.26	2.31 and 2.34[b]
1-methyl-(4-methoxybenzene) methanol	1.55 and 1.61	3.45 and 3.55	insep.	3.79 and 3.80[c]

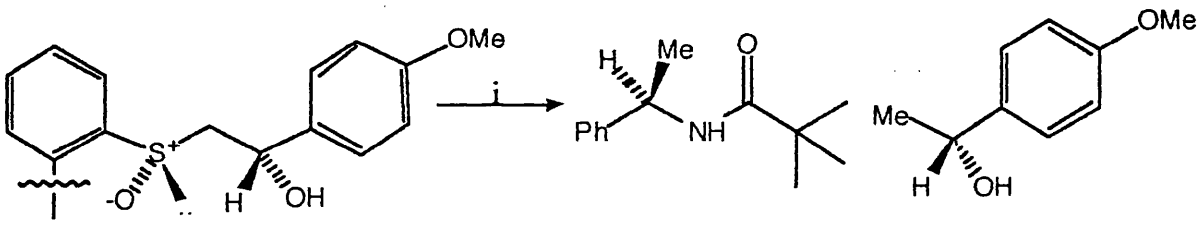
a. *tert*-Butyl protons; b. Aromatic methyl protons; c. Aromatic methoxy.

Proton resonances from the racemic Mosher esters derived from (R)-(+)-MTPA and alcohols furnished by sodium borohydride reduction of the corresponding ketones.

Table 26

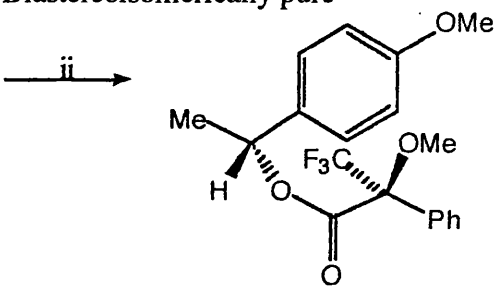
Proton NMR examination of the ester mixture displayed distinct signals for the proton resonances for each diastereoisomer (table 26).

A means for the determination of enantiomeric excess of the cleaved alcohols had been achieved thus the study of the cleavage of diastereoisomerically pure β-hydroxysulphoxides was undertaken. Treatment of optically pure ($S_{(S)}$ R, R)-(-)-(**100**) with Raney™ nickel in aqueous tetrahydrofuran resulted in the formation of an equimolar reaction mixture of amide (R)-(+)-(**60**) and alcohol (R)-(**110**). Reaction of this mixture with (R)-(+)-MTPA under DCC coupling conditions gave a mixture of unreacted amide (R)-(+)-(**60**) and MTPA ester (**111**) (Scheme 89).



($S_{(S)}$ R, R)-(-)-(**100**) (R)-(+)-(**60**) (R)-(**110**)

Diastereoisomerically pure



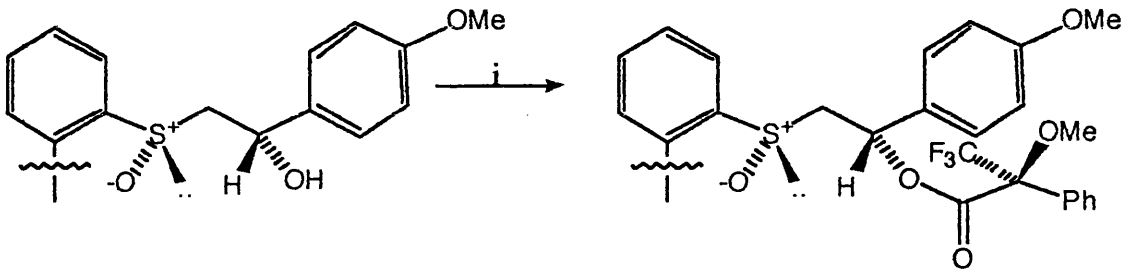
(**111**)

i Raney™ nickel, 10% aqueous tetrahydrofuran, ii R-(+)-MTPA, DCC, 4-dimethylaminopyridine,chloroform, ambient temperature, 16h.

Scheme 89

Examination of the crude reaction mixture by ^1H NMR spectroscopy showed full consumption of (R)-(**110**) and determined that ester (**111**) had a diastereoisomeric excess (for signals for major diastereoisomer see table 27) of only 81%, a reduction of up to 19%. To confirm that there was no epimerisation occurring in the condensation of alcohol (R)-(**100**) and the (R)-(+)-MTPA, diastereoisomerically pure ($S_{(S)}$ R, R)-

(-)-(**100**) was acylated under standard conditions (Scheme 90). The MTPA ester (**112**) was isolated as a single stereoisomer proven by ^1H NMR spectroscopy. It is unlikely that the observed epimerisation occurred in the coupling reaction with (R)-(+)-MTPA, thus the racemisation must happen in the Raney™ nickel reduction step.



($S_{(S)}$ R, R)-(-)-(**100**) (**112**)

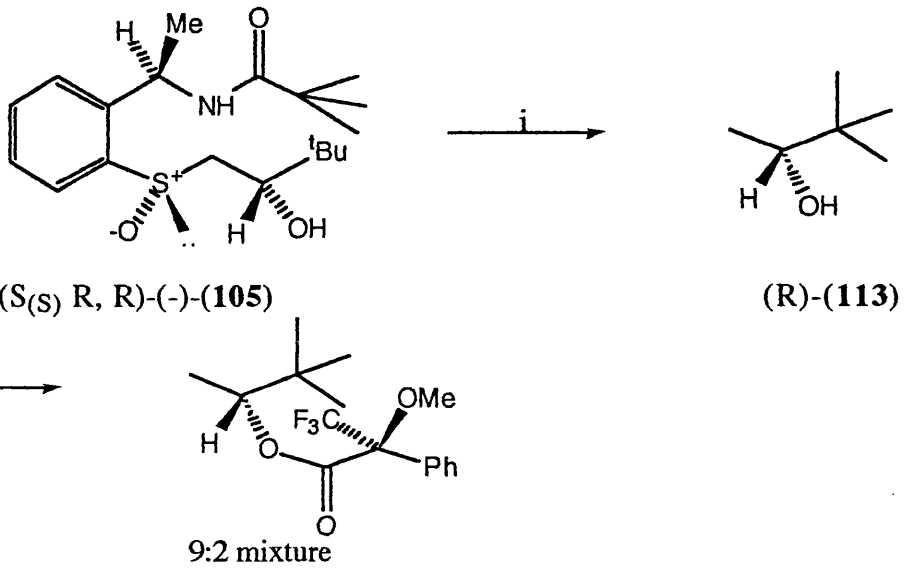
Diastereoisomerically pure Single diastereoisomer

i R-(+)-MTPA, DCC, 4-dimethylaminopyridine,chloroform, ambient temperature, 16h.

Scheme 90

Further studies were undertaken to determine whether the phenomena was restricted to ($S_{(S)}$ R, R)-(-)-(**100**). Reaction of diastereoisomerically pure ($S_{(S)}$ R, R)-(-)-(**102**) under the same conditions as outlined above, generated a reaction mixture containing the amide (R)-(+)-(**60**) and a trace (<10%) of the required alcohol. Treament of this reaction mixture with (R)-(+)-MTPA and DCC resulted in the formation of a 1:1 mix of isomers. The small trace of alcohol generated in the cleavage was racemic!

Diastereomerically pure ($S_{(S)}$ R, R)-(-)-(**105**) upon treament with Raney™ nickel gave an equimolar reaction mixture containing (R)-(+)-(**60**) and alcohol (R)-(**113**). Reaction of the resultant mixture with (R)-(+)-MTPA resulted in the formation of a 9:2 mixture of epimeric esters (Scheme 91 and table 27).



($S_{(S)}$ R, R)-(-)-(**105**) (R)-(**113**)

9:2 mixture

i Raney™ nickel, 10% aqueous tetrahydrofuran, ii R-(+)-MTPA, DCC, 4-dimethylaminopyridine,chloroform, ambient temperature, 16h.

Scheme 91

Alcohol	Methyl	Methoxy	Methyne	Other
3,3-dimethylbutan-2-ol	1.19	3.51	4.85	0.90[a]
1-methyl-(4-methoxybenzene) methanol	1.56	3.45	insep.	3.81[b]

a. *tert*-Butyl protons; b. Aromatic methoxy.

Proton resonances of the major diastereoisomer from the Mosher esters derived from (R)-(+)-MTPA and alcohols; furnished by Raney™ nickel reduction of the corresponding *cis*-β-hydroxysulphoxides.

Table 27

The major ester stereoisomer from the cleavage of ($S_{(S)}$ R, S)-(-)-(**105**) was shown to be derived from (R)-(**113**) by comparison with literature[99] data. The isolation of (R)-(**113**) derived ester was proof for the DIBAL-H zinc (II) bromide reduction of ($S_{(S)}$ R)-(-)-(**88**) generating ($S_{(S)}$ R, R)-(-)-(**105**).

Raney™ nickel reduction methodology cannot be applied in this case since the alcohol products were shown to be of low enantiomeric excess . A possible pathway for

epimerisation could go *via* the known[101] oxidation of alcohols to the corresponding ketones. A small amount of the cleaved alcohol could undergo this oxidation followed by reduction[102] to the racemic alcohol thus lowering the observed enantiomeric excess of the cleaved alcohol.

Reaction of the *cis*-β-hydroxysulphoxides with the milder nickel boride[103] (generated *in situ* from sodium borohydride and nickel (II) chloride) proceeded to give the same degree of racemisation of the desulphurised alcohol.

The reductive methodology described above has a second drawback within the context of the project. Removal of the sulphur from the amide side-chain destroyed any means of regenerating the sulphoxide source ($S_{(S)}$ R)-(+)-*cis*-(**59**) *via* sulphinic acid (R)-(-)-(**61**).

2.5 Chemistry of the Cyclic β-Ketosulphoxides.

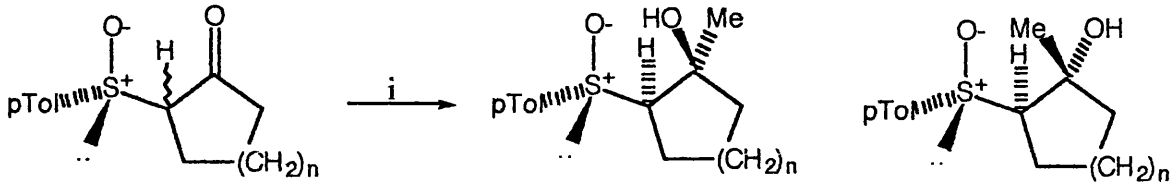
With the lack of progress in the removal of the sulphinyl unit from the acyclic β-hydroxysulphoxides attention was turned towards utilising the readily synthesised cyclic β-ketosulphoxides.

2.5.1 Nucleophilic attack upon cyclic β-ketosulphoxides.

The attack of hydride and methyl (*via* trimethylaluminium) nucleophiles on C-2 substituted and cyclic β-ketosulphoxides have been studied by many workers. Garcia Ruano and co-workers[104] have reported the reaction of 2-p-toylsulphinylcycloalkanones with trimethylaluminium (Scheme 93).

Treatment of diastereoisomerically pure ($S_{(S)}$)-(**114**) with trimethylaluminium resulted in the formation of a mixture of epimeric hydroxysulphoxides ($S_{(S)}$ S)-(**115**) and ($S_{(S)}$ R)-(**116**) (table 28). The subsequent reaction of an epimeric (at C-2) sample of ($S_{(S)}$)-(**114**) resulted in the generation of the same ratio of ($S_{(S)}$ S)-(115) and ($S_{(S)}$ R)-(**116**) (table 28). These results were mimicked by the reaction of the corresponding

cyclopentanone derivative ($S_{(S)}$)-(**117**) in generating($S_{(S)}$ S)-(**118**) and ($S_{(S)}$ R)-(**119**).



n=2 ($S_{(S)}$)-(**114**) ($S_{(S)}$ S)-(**115**) ($S_{(S)}$ R)-(**116**)

n=1 ($S_{(S)}$)-(**117**) ($S_{(S)}$ S)-(**118**) ($S_{(S)}$ R)-(**119**)

i Trimethylaluminium, toluene, ambient temperature.

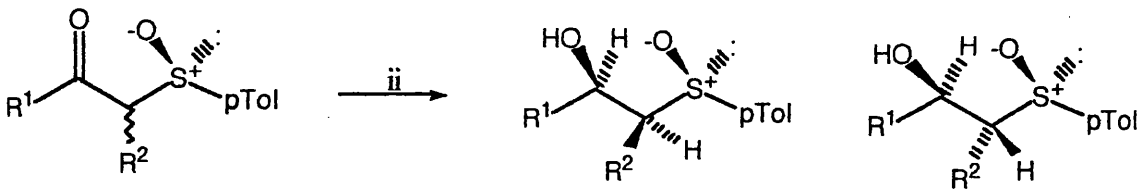
Scheme 93

Ketone	Diastereoisomeric purity of ketone	n=2; (115):(116) n=1; (118):(119)	Yield %
(114)	99:1	80:20	95
(114)	75:25	80:20	95
(117)	99:1	99:1	98
(117)	78:22	99:1	96

Reaction of cyclic β-ketosulphoxides ($S_{(S)}$)-(114) and ($S_{(S)}$)-(117) with trimethylaluminium.

Table 28

The same group[105] have also investigated the DIBAL-H reduction of simple C-2 substituted acyclic β-ketosulphoxides with the results of this study outlined in table 29 and scheme 94.



ii DIBAL-H, tetrahydrofuran, -78°C.

Scheme 94

R^1	R^2	Epimeric ratio	Hydroxysulphoxide ratio	Yield
Me	Me	66:34	66:34	91
n-Pr	Me	60:40	60:40	98
n-Pr	Bn	55:45	60:40	73
n-Pr	Allyl	60:40	60:40	77
i-Pr	Me	70:30	69:31	93

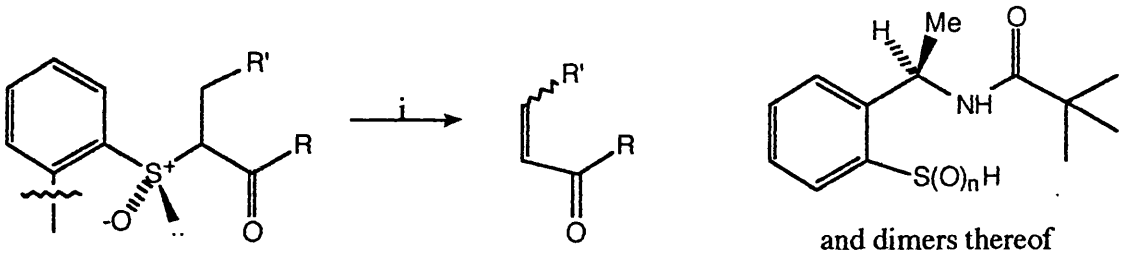
Reaction of epimeric β-ketosulphoxides with DIBAL-H.

Table 29

The main conclusion to be drawn from both pieces of work was that the sulphur stereocentre exhibited a greater influence than the C-2 stereocentre in the stereodirection of asymmetric processes at the carbonyl.

2.5.2 Synthesis of cyclic enones *via* thermal elimination of cyclic β-ketosulphoxides.

From work carried out within the department, it has been found[106] that though stable in the solid state ($S_{(S)}$ R)-(+)-*cis*-(**59**) derived cyclic β-ketosulphoxides undergo facile sulphenic acid elimination to generate the analogous enones in solution (Scheme 95 and table 30).



and dimers thereof

i Toluene, sodium hydrogen carbonate, 60°C, 2-3h,

Scheme 95

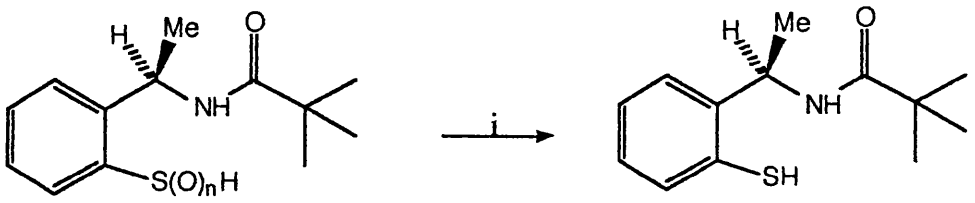
R	R'	Yield of enone %	*cis* : *trans*
Ph	H	60	-
$-(CH_2)_3-$		84	*cis*
$-(CH_2)_4-$		80	*cis*
$-(CH_2)_7-$		98	4 : 96
$-(CH_2)_{12}-$		72	*trans*
$-[(CH_2)_2(CHMe)]-$		50	*cis*

Elimination of C-2 substituted and cyclic β-ketosulphoxides derived from ($S_{(S)}$ R)-(+)-*cis*-(59) to generate enones.

Table 30

The optimised conditions were found to be 60°C in toluene, in the presence of sodium hydrogen carbonate acting[107] as an acid scavenger. The conditions outlined are milder than reported elimination techniques[108] which involved considerably higher temperatures (up to refluxing dichlorobenzene) and the enones formed were subject to Michael addition of the generated sulphenic acid.[109]

The sulphinyl residues from the elimination of ($S_{(S)}$ R)-(+)-*cis*-(**59**) derived β-ketosulphoxides were recovered as a complex mixture of sulphur compounds which existed at a variety of oxidation states. Treatment of these residues with triphenylphosphine and iodine[90] resulted in conversion to the thiol (R)-(+)-(**70**) in good yield (Scheme 96).



and dimers (R)-(+)-(**70**)

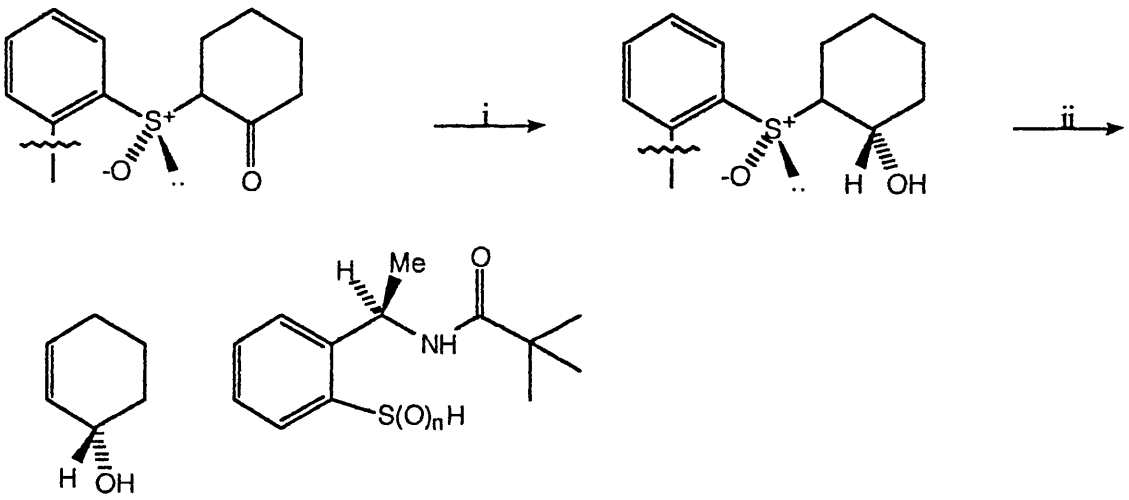
i Triphenylphosphine, iodine, chloroform, toluene, ambient temperature, 2h

Scheme 96

From both this elimination protocol and the previously described aldol chemistry the sulphinyl unit was recovered as (R)-(+)-(**70**) which would require oxidation to acid (R)-(-)-(**61**) to fulfill the main aim of the project - a recyclable source of homochiral sulphoxide.

2.5.3 Asymmetric synthesis of enantiomerically enriched cyclic allylic alcohols.

With the two pieces of information in hand, the proposal that a stereochemically sulphoxide defined reduction of cyclic β-ketosulphoxides followed by a ready sulphoxide elimination would furnish cyclic allylic alcohols of high enantiomeric purity was examined (Scheme 97).[110]

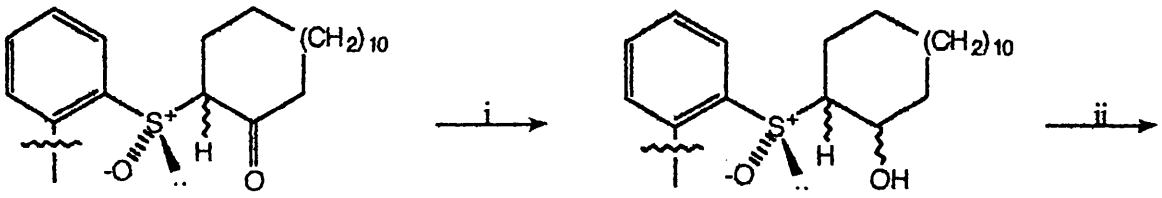


i Stereocontrolled reduction mediated by the sulphoxide, ii Thermal elimination.

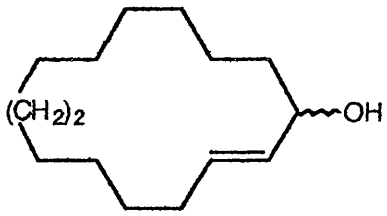
Scheme 97

Further reduction of the sulphinyl residues would give thiol (R)-(+)-(**70**) which at a later date could be elaborated to sulphinic acid (R)-(-)-(**61**).

Towards meeting this aim, the cyclopentadecanone derived cyclic β-ketosulphoxide ($S_{(S)}$ R)-(**95**) was treated with sodium borohydride in methanol. The resultant crude reaction mixture was heated at 60°C in toluene in the presence of one equivalent of sodium hydrogen carbonate for 16h. Column chromatography of the crude mixture resulted in the isolation of the allylic alcohol[111] (**120**) in 77% yield (from ($S_{(S)}$ R)-(**95**)) (Scheme 98).



$(S_{(S)}\ R)$-(**95**)



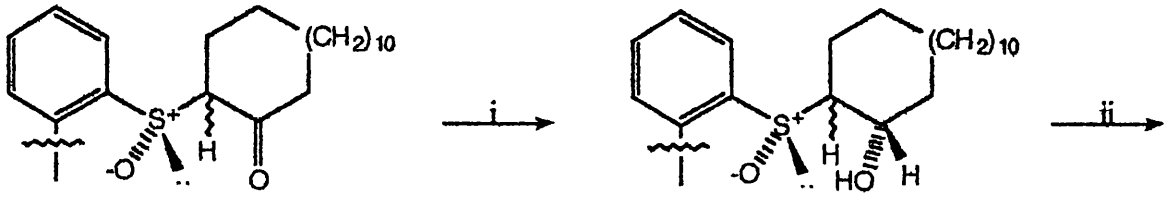
(120)

i Sodium borohydride, methanol, 0°C, ii Toluene, sodium hydrogen carbonate, 60°C, 16h.

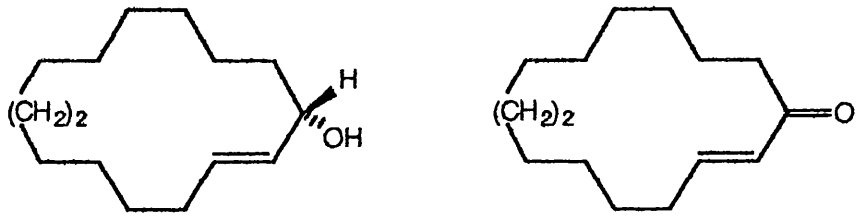
Scheme 98

Conversion of the alcohol to the corresponding MTPA ester showed that the allylic alcohol generated was racemic.

Subsequently ketone $(S_{(S)}\ R)$-(**95**) was treated with zinc (II) bromide followed by DIBAL-H at -78°C following the standard procedure. The resultant crude product from the reduction was heated in toluene under the devised elimination conditions. Flash column chromatography of the subsequent mixture resulted in the isolation of two new products. The product (12%) with the higher r_f was identified as enone (**121**) by comparison to the earlier work carried out in the group. The enone must be a product of the thermal elimination of unreduced ketone $(S_{(S)}\ R)$-(**95**) The second spot was the required allylic alcohol (S)-(-)-(**120**), isolated in 82% yield (Scheme 99). Alcohol (S)-(-)-(**120**) was found to have an optical rotation of -20.9° (c=4.85, chloroform), proving that (S)-(-)-(**120**) was optically active. Transformation of (R)-(-)-(**120**) to the required MTPA ester (**122**) showed that an enantiomeric excess of 88% (assessed by ^1H NMR spectroscopic techniques) had been achieved in the process.



$(S_{(S)}\ R)$-(**95**)

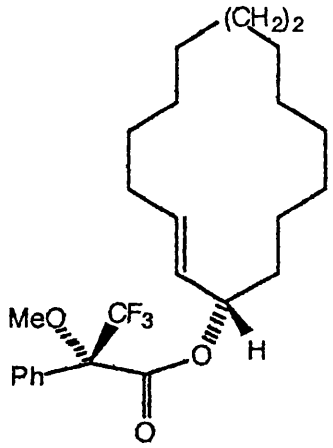


(S)-(-)-(**120**) (**121**)

82% 12%

i DIBAL-H, zinc (II) bromide, tetrahydrofuran, -78°C, ii Toluene, sodium hydrogen carbonate, 60°C, 16h.

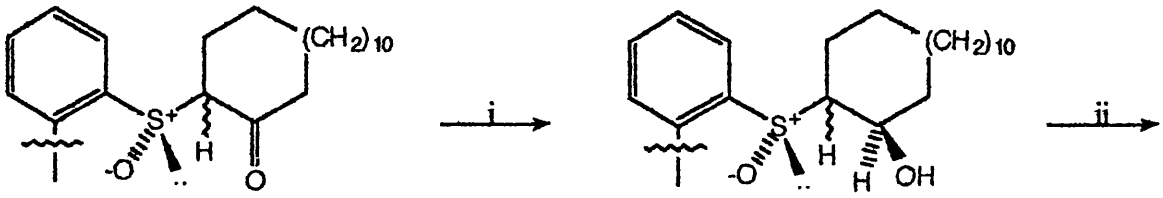
Scheme 99



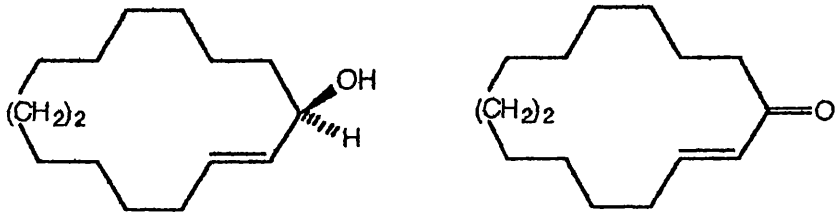
(**122**)

With this result achieved $(S_{(S)}\ R)$-(**95**) was treated with DIBAL-H in tetrahydrofuran in the same fashion as the analogous acyclic β-ketosulphoxides. The resultant crude reaction was then treated under the previously described elimination conditions (Scheme 100). Again two spots were recovered, (**121**) isolated in 20% yield and (R)-(+)-(**120**) in 44% yield. The overall yield in the case of this reaction was lower than

that achieved in the DIBAL-H zinc (II) bromide reaction. Full elimination of the reduced material was confirmed by t.l.c of the crude reaction mixture.



$(S_{(S)}\ R)$-(**95**)



(+)-(**120**) (**121**)

44% 20%

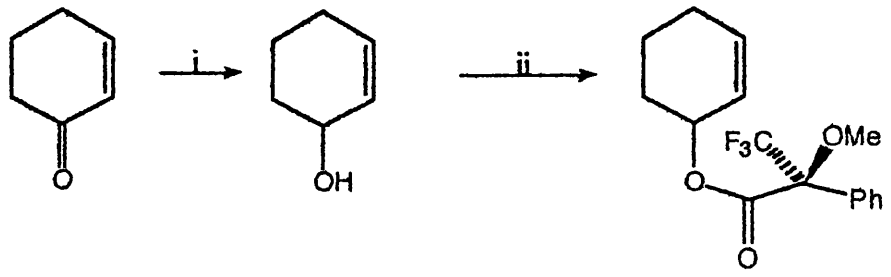
i DIBAL-H, tetrahydrofuran, -78°C, ii Toluene, sodium hydrogen carbonate, 60°C, 16h.

Scheme 100

Treatment of alcohol (R)-(+)-(**120**) with (R)-(+)-MTPA resulted in the formation of the ester (**123**) with a diastereoisomeric excess of only 12%. The major diastereoisomer formed in the DIBAL-H case was opposite to that obtained with the DIBAL-H zinc (II) bromide protocol by comparison of the ^{1}H NMR spectra of the two corresponding MTPA esters.

Ketone $(S_{(S)}\ R)$-(**92**) was chosen as the next cyclic β-ketosulphoxide to demonstrate the methodology.

Treatment of 2-cyclohexenone (**124**) under Luche[112] reduction conditions followed by reacting the generated allylic alcohol (±)-(**125**) with (R)-(+)-MTPA and DCC resulted in the formation of the diastereoisomeric pair of Mosher esters (Scheme 101).



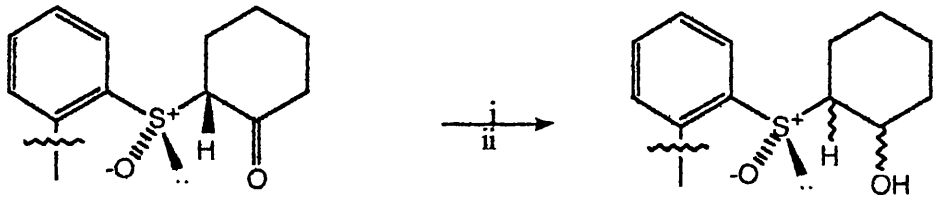
(124) **(±)-(125)**

i Sodium borohydride, cerium (III) chloride, methanol, ii R-(+)-MTPA, dicyclohexylcarbodiimide, 4-dimethylaminopyridine, chlorofrom, 16h.

Scheme 101

Examination of the ^1H NMR spectra of the esters showed distinct signals corresponding to the vinyl protons of each diastereoisomer thus a means for assesing the enantiomeric excess of the generated allylic alcohol (**125**) was achieved.

Sodium borohydride reduction of (**92**) resulted in formation of epimeric (**126**) but heating epimeric (**126**) in toluene at 60°C for 16h resulted in the recovery of unreacted (**126**). Prolonged reaction time or elevated temperatures failed to generate any (**125**) (Scheme 102).



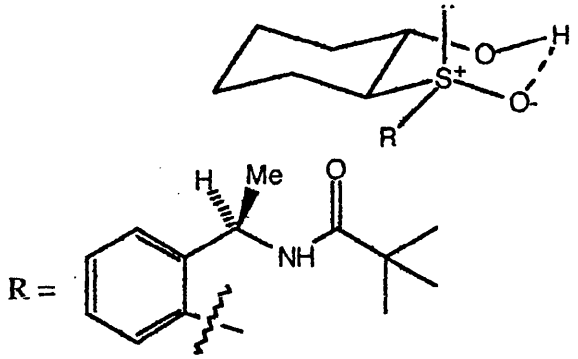
($S_{(S)}$ R)-(92) **(126)**

i Sodium borohydride, methanol, 0°C, ii Toluene, 60°C-reflux, sodium hydrogen

ii Sodium borohydride, methanol, 0°C, ii Toluene, 60°C-reflux, sodium hydrogen carbonate, 16h+.

Scheme 102

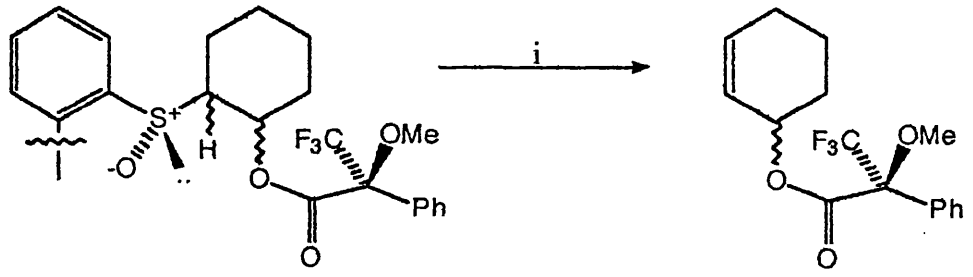
From examination of the literature for similar systems it had been suggested[113] that the presence of a hydrogen bonded intermediate (figure 17) could prevent the required sulphoxide *syn* orientation which would lead to the required elimination.



Possible hydrogen bonded intermediate preventing *syn* elimination.

Figure 17

The ability to generate the hydrogen bond was removed by acylation of the alcohol (**126**) with (R)-(+)-MTPA under standard coupling conditions. Thermal elimination of epimeric ester (**127**) occurred in refluxing toluene generating a 1:1 epimeric mixture of allylic esters in 80% yield (Scheme 103).



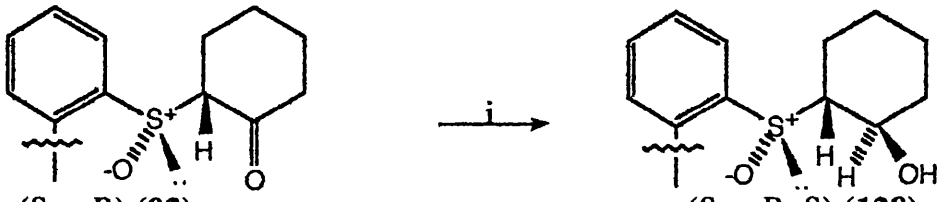
(**127**) 1:1 mixture

80%

i Toluene, sodium hydrogen carbonate, reflux, 16h.

Scheme 103

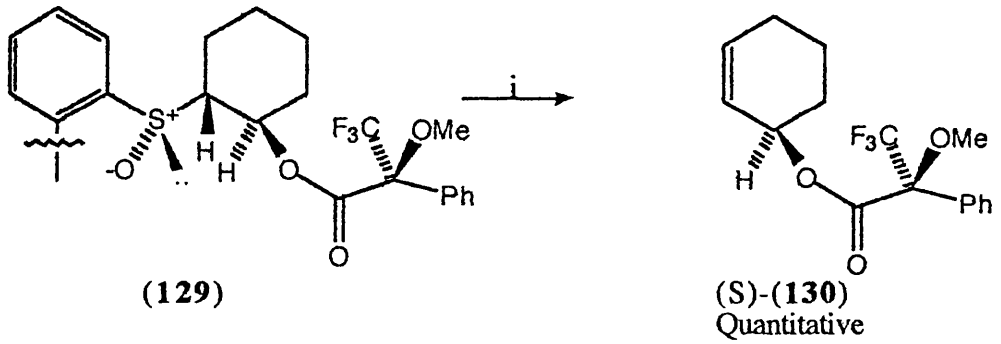
DIBAL-H reduction of ($S_{(S)}$ R)-(**92**) proceeded in poor yield (31%) to generate a single stereoisomer (by ^1H NMR spectroscopy) of ($S_{(S)}$ R, S)-(**128**) (Scheme 104). The remaining mass balance was recovered as unreduced ketone ($S_{(S)}$ R)-(**92**). The reason for this poor reactivity lay in the low solubility of ($S_{(S)}$ R)-(**92**) in the reaction solvent.



i DIBAL-H, tetrahydrofuran, -78°C.

Scheme 104

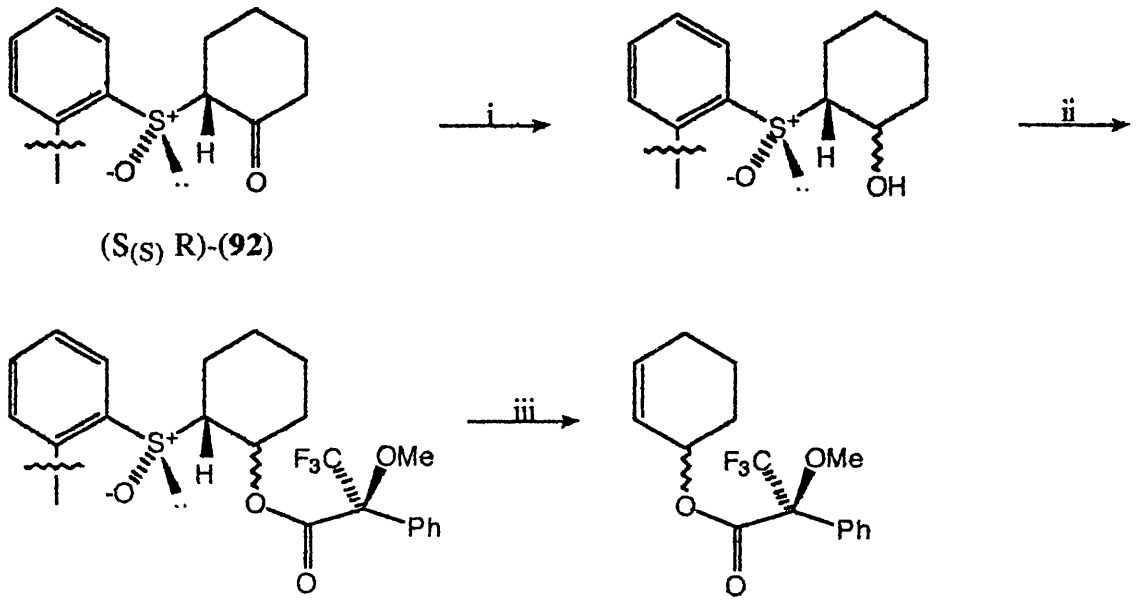
Conversion of ($S_{(S)}$ R, S)-(**128**) to MTPA ester (**129**) was achieved in 75% yield and thermal elimination of (**129**) in refluxing toluene resulted in the formation of the allylic ester (S)-(**130**) in quantitative yield as a single stereoisomer (Scheme 105).



i Toluene, sodium hydrogen carbonate, reflux, 16h.

Scheme 105

DIBAL-H zinc (II) bromide reduction of ($S_{(S)}$ R)-(**92**) resulted in the isolation of a 1:1 epimeric product in 82% yield, R-(+)-MTPA derivatisation generated the diastereoisomeric esters in 50% yield. Subsequent thermal elimination of the mixture resulted in the isolation of a 1:1 mixture of diastereoisomeric allylic esters in 54% yield (Scheme 106).



($S_{(S)}$ R)-(**92**)

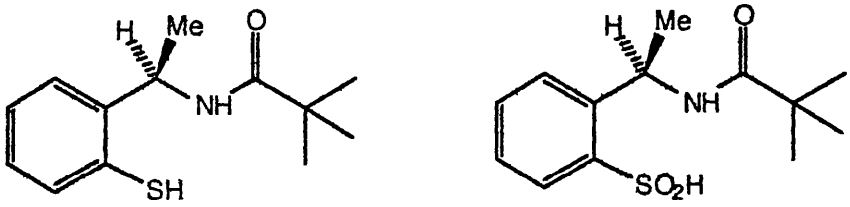
i DIBAL-H, zinc (II) bromide, tetrahydrofuran, -78°C, ii.R-(+)-MTPA, dicyclohexylcarbodiimide, 4-dimethylaminopyridine, chlorofrom, 16h, iii Toluene, sodium hydrogen carbonate, reflux, 16h.

Scheme 106

2.6 Regeneration of the Sulphoxide Source ($S_{(S)}$ R)-(+)-*cis*-(59)

With the completion of the sulphoxide mediated chemistry, the last step in the synthetic sequence required regeneration of source ($S_{(S)}$ R)-(+)-*cis*-(**59**) *via* sulphinic acid (R)-(-)-(**61**).

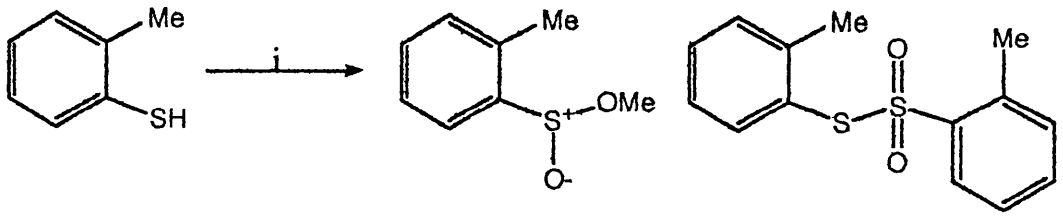
From the chemistry outlined in the previous sections the sulphur moiety from the reductive removal was isolated as thiol (R)-(+)-(**70**). Therefore a method was required to effect the required oxidation from (R)-(+)-(**70**) to acid (R)-(-)-(**61**).



(R)-(+)-(**70**) (R)-(-)-(**61**)

2.6.1 Model studies for the oxidation.

2-Thiocresol (**131**) was selected as a model substrate since it contained some degree of steric hindrance around the aromatic thiol. Thiol (**131**) was treated with sodium periodate[114] in 10% aqueous methanol at room temperature for 16h. From examination of the ^1H NMR spectra of the crude reaction mixture two new compounds had been generated (Scheme 107). The more polar compound was assigned the structure of methyl sulphinate (75% yield) (**132**) and the less polar component of the mixture as thiosulphonate (20% yield) (**133**).



(131) **(132)** 75% **(133)** 20%

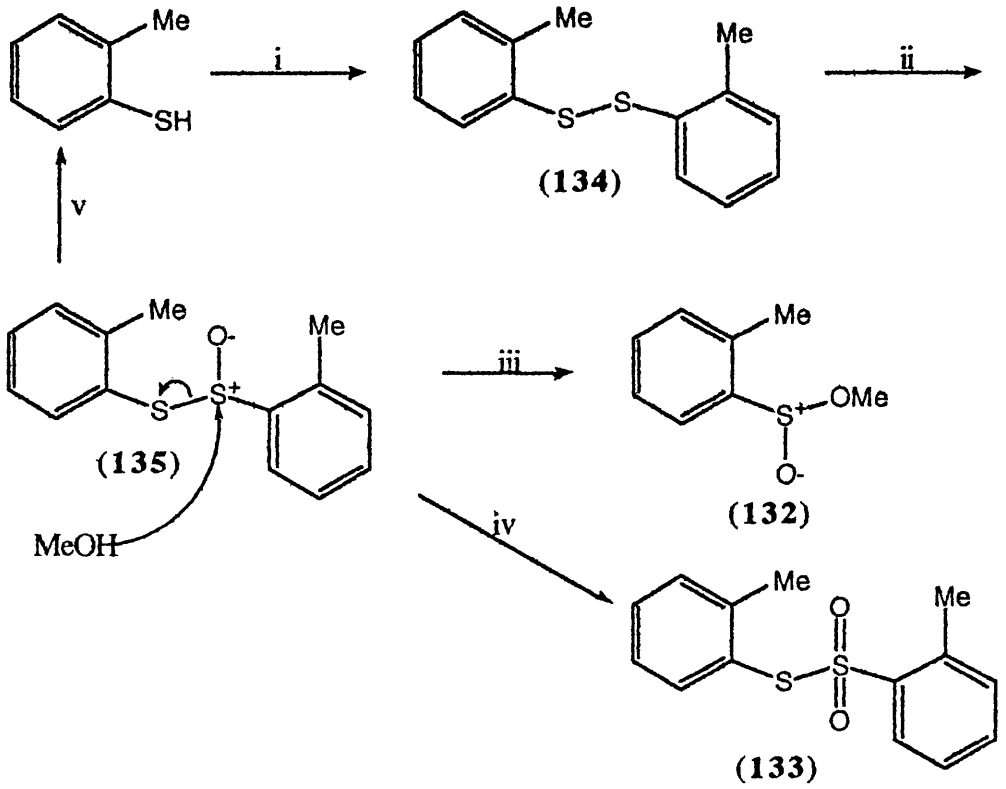
i Sodium periodate, 10% aqueous methanol, 16h.

Scheme 107

The mechanism for this oxidation was proposed to involve initial oxidation of (**131**) to generate disulphide (**134**) (Scheme 108). Disulphide (**134**) underwent oxidation generating thiosulphinate (**135**) at which point two possible divergent pathways were possible;

a) Cleavage of the sulphur-sulphur bond in (**135**) by the nucleophilic solvent to give major product (**132**),

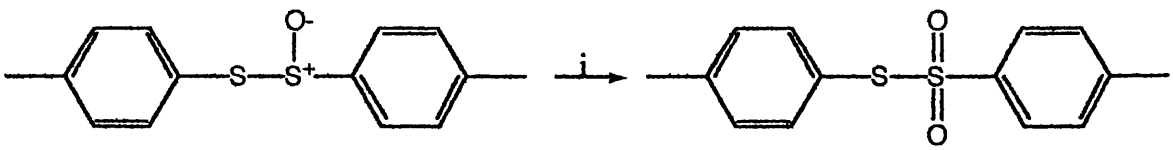
b) Further oxidation of the thiosulphinate to give minor product (**133**).



i Oxidation of (**131**) to (**134**), ii Oxidation to the thiosulphinate (**135**), iii Nucleophilic attack of methanol on (**135**) (path a), iv Oxidation of (**135**) to (**133**) (path b), v Re-entry of (**131**) to oxidation pathway after step iii,

Scheme 108

Literature precedent agreed with this proposed mechanism, Oae[115] and co-workers had shown that sodium periodate oxidation of thiosulphinates (**136**) in aqueous solvents generated the corresponding thiosulphonates (**137**) in high yield (Scheme 109).



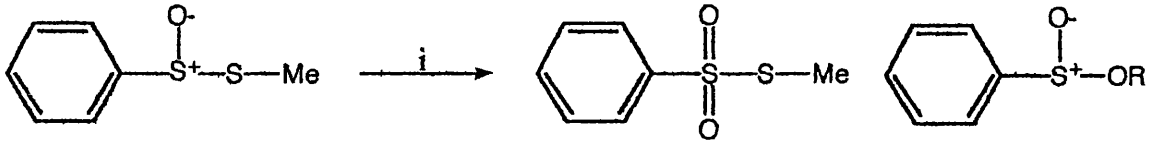
(**136**) (**137**)

i Sodium periodate, aqueous dioxan,

Scheme 109

Further studies by this group[116] gave an insight into pathway a) described in scheme 108. Treatment of unsymmetrical thiosulphinate (**138**) in aqueous alcoholic solvents

with sodium periodate resulted in the formation of a mixture of sulphinate ester (**139**) and thiosulphonate (**140**), the mixture composition dependant on the alcohol (Scheme 110 and table 31).



(138) **(140)** **(139)**

i Sodium periodate, aqueous alcohol.

Scheme 110

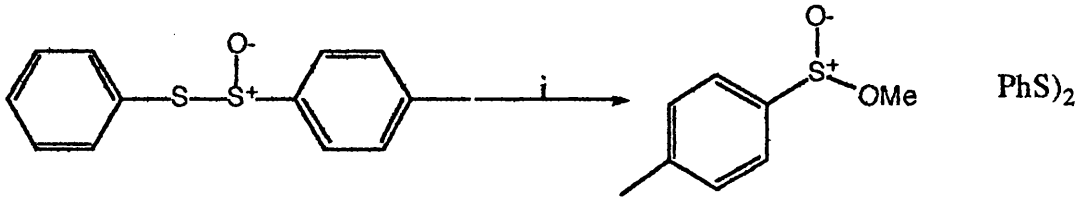
Alcohol	Yield of (139)	Yield of (140)
Ethanol	39	42
iso-Propanol	27	67
tert-Butanol	7	82

Sodium periodate and aqueous alcohol oxidation of (138).

Table 31

Reduction in the size of the alcohol increased the amounts of (**139**) produced. In the reported study methanol was not investigated so extrapolating from the available data methanol would give the highest amount of (**132**), *via* pathway a).

These workers[117] reported the use of methanol as solvent in the presence of a catalytic amount of iodine or bromine in the conversion of thiosulphinate (**141**) to the corresponding methyl sulphinate ester (**142**) (Scheme 111).



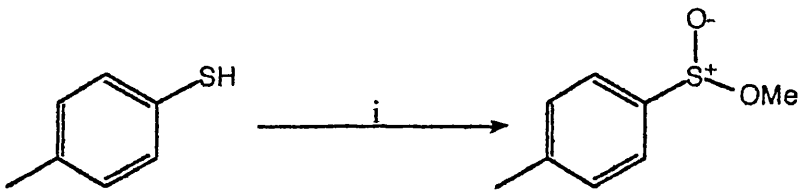
(141) **(142)**

91%

i Iodine or bromine, methanol.

Scheme 111

Application of the combined iodine and sodium periodate methodologies to oxidation of 4-thiocresol (**143**) resulted in oxidation to solely the methyl sulphinate (**142**), as judged by examination of the crude reaction mixture by ^{1}H NMR spectrocopy (Scheme 112).



(143) **(142)**

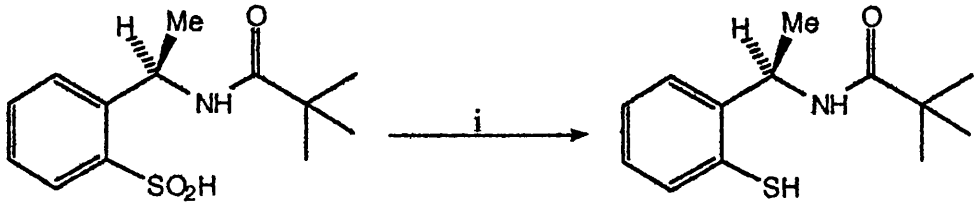
i Sodium periodate, 10% iodine, 10% aqueous methanol.

Scheme 112

This methodology represented a novel means for effecting the oxidation of aromatic thiols to the corresponding methyl sulphinates.

2.6.2 Application to thiol (R)-(+)-(**70**).

Before the oxidation studies of thiol (R)-(+)-(**70**) could be undertaken, a quantity of thiol was required. Sulphinic acid (R)-(-)-(**61**) was reduced with triphenylphosphine and iodine[90] in a mixed solvent of toluene and chloroform to generate (R)-(+)-(**70**) in 90% yield contaminated with 8% of (**73**) (Scheme 113).



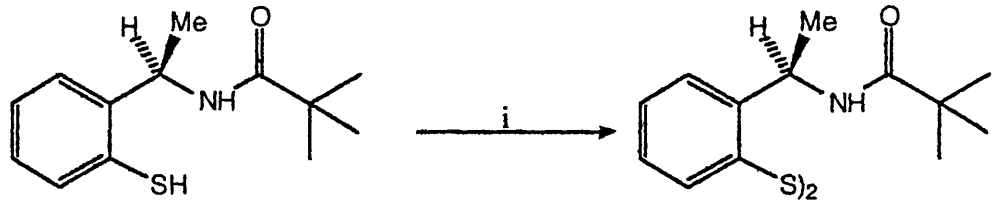
(R)-(-)-(**61**) (R)-(+)-(**70**)

90%

i Triphenylphosphine, iodine, toluene and chloroform.

Scheme 113

With sufficient quantities of (R)-(+)-(**70**) in hand, oxidation of (R)-(+)-(**70**) could be undertaken. Treatment of the thiol with the sodium periodate protocol resulted in the sole formation of (**73**). Extended reaction time or additional oxidant produced no further oxidation (Scheme 114).

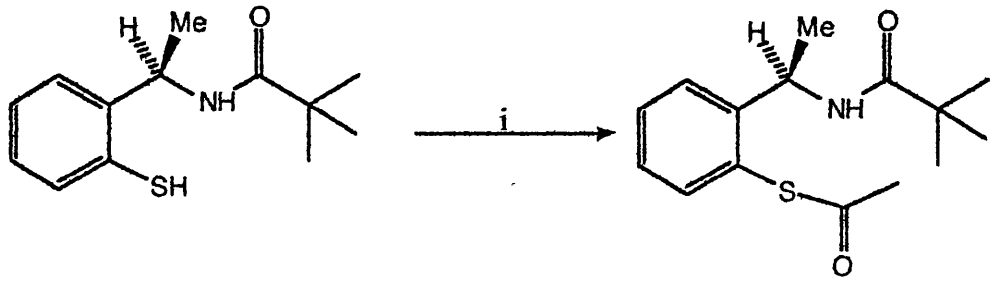


(R)-(+)-(**70**) (**73**)

i Sodium periodate, 10% aqueous methanol.

Scheme 114

In the aftermath of this unexpected result other possible oxidation protocols were studied. Thea and co-workers[118] had reported that treatment of thioacetates with sulphuryl chloride in acetic anhydride generated the corresponding sulphinyl chlorides. If such a sulphinyl chloride was generated from (R)-(+)-(**70**), spontaneous ring closure would generate sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**). Thiol (R)-(+)-(**70**) was sequentially treated with sodium hydride and acetyl chloride to generate (R)-(**144**) in quantitative yield (Scheme 115).



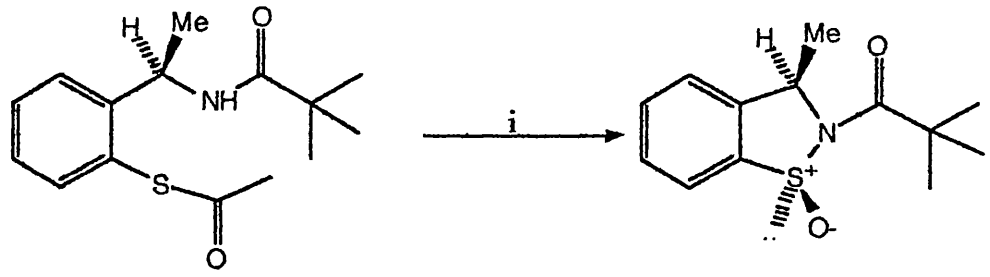
(R)-(+)-(**70**) (R)-(**144**)

Quantitative

i Sodium hydride, acetyl chloride, tetrahydrofuran.

Scheme 115

Reaction of acetate (**144**) in accordance with the reported conditions gave a complex reaction mixture. Careful flash column chromatography resulted in the isolation of sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) as a single stereoisomer, but in only 13% yield (Scheme 116).



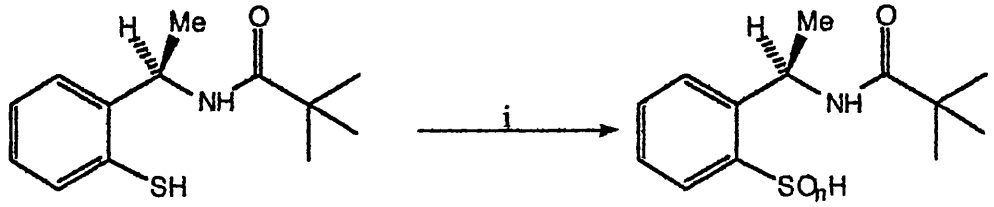
(R)-(**144**) ($S_{(S)}$ R)-(+)-*cis*-(**59**)

13%

i Sulphuryl chloride, acetic anhydride, toluene.

Scheme 116

Basic hydrogen peroxide[119] has been reported to perform the selective oxidation of thiols to the analogous sulphinic acids. Treatment of (R)-(+)-(**70**) resulted in the formation of an equimolar mixture of sulphinic and sulphonic acids (Scheme 117).



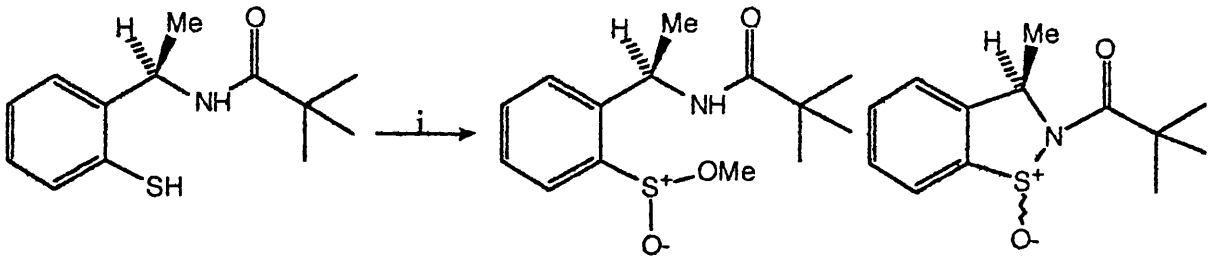
(R)-(+)-(**70**) n=2 and 3

i Hydrogen peroxide, sodium hydroxide, ethanol.

Scheme 117

The application of other oxidation[120] protocols only achieved oxidation to the corresponding disulphide with no further oxidation observed.

In an attempt to increase the rate of the original sodium periodate oxidation, the reaction was repeated in refluxing aqueous methanol. Examination of the crude reaction mixture by thin layer chromatography revealed the formation of two new products (Scheme 118). After column chromatography, the two new compounds were isolated and identified as a 1:1 epimeric mixture of methyl sulphinate (R)-(**145**) in 66% yield and epimeric sulphinamide (34%) (**59**) in a 15:2 ratio (($S_{(S)}$ R)-(+)-*cis*-(**59**) predominated).



(R)-(+)-(**70**) (R)-(**145**) (**59**)

66% (1:1) 34% (15:2)

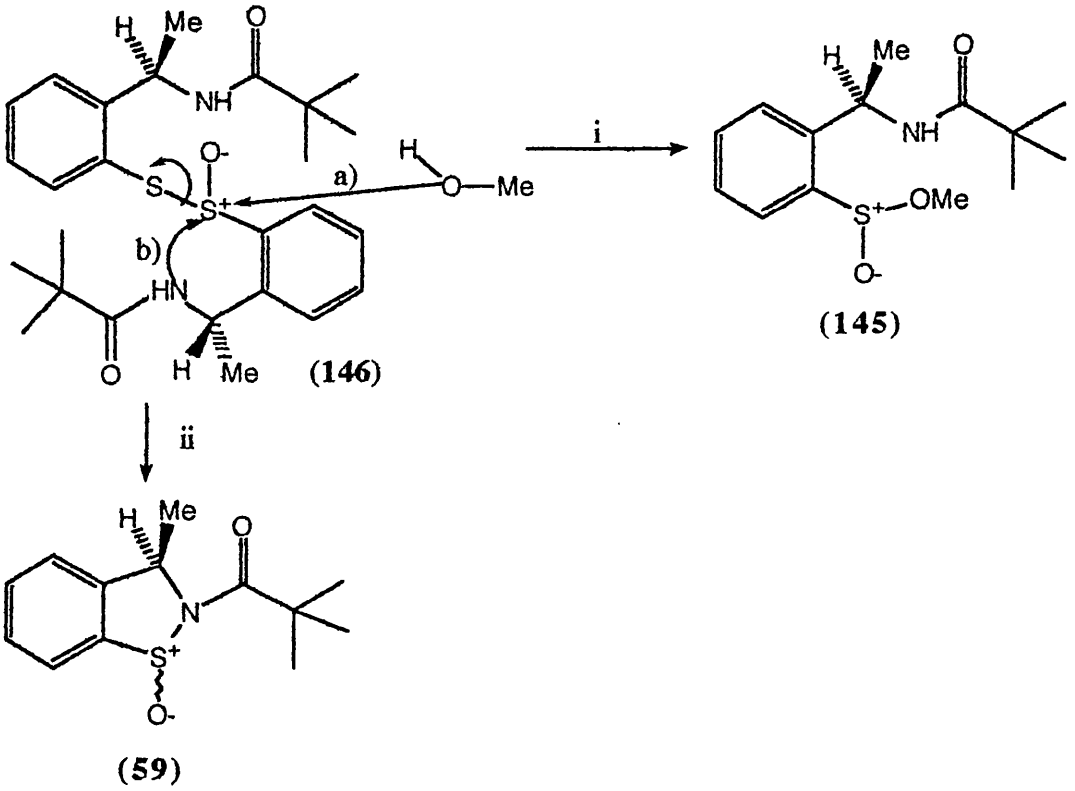
i Sodium periodate, 10% aqueous methanol, reflux, 16h.

Scheme 118

Formation of epimeric (**59**) could be rationalized by proposing that upon formation of thiosulphinate intermediate (**146**), two possible reaction routes could be followed (Scheme 119);

a) Simple nucleophilic attack by methanol resulted in the formation of (**145**).

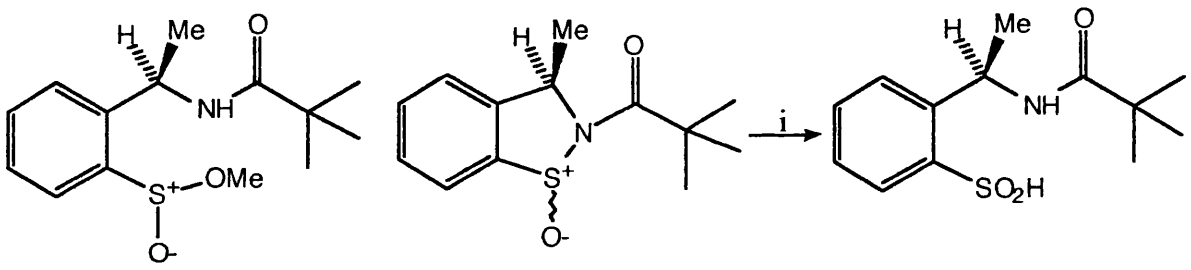
b) Intermediate (**146**) could undergo intramolecular trapping by the nucleophilic amide to generate the epimeric (**59**).



i Methanolysis, ii Amide trapping.

Scheme 119

In an attempt to confirm that epimeric (**59**) was derived from intramolecular ring closure of (**146**) and not due to (R)-(**145**) undergoing subsequent cyclisation, (R)-(**145**) was heated at reflux in methanol. Examination of the reaction mixture showed no epimeric (**59**), hence (**145**) did not undergo thermal cyclisation to generate (**59**). Treatment of a tetrahydrofuran solution of (R)-(**145**) and (**59**) (direct from the oxidation) with aqueous sodium hydroxide solution (2 molar) gave acid (R)-(-)-(**61**) in 82% yield from (R)-(+)-(**70**) (Scheme 120).



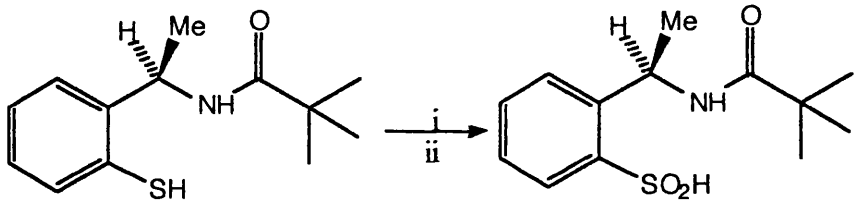
(R)-(**145**) (**59**) (R)-(-)-(**61**)

82%

i Aqueous sodium hydroxide (2 molar), tetrahydrofuran, 2h.

Scheme 120

Closer examination of the literature yielded another possible method for the generation of (**145**). Brownbridge[121] had reported that treatment of disulphides with potassium carbonate and n-bromosuccinimide in methanol resulted in the formation of methyl sulphinates in good to excellent yields. Thiol (R)-(+)-(**70**) was treated with potassium carbonate and n-bromosuccinimide in methanol and the intermediate ester (**145**) was immediately subjected to the hydrolysis conditions resulting in the formation of acid (R)-(-)-(**61**) in 80% yield (Scheme 121).



(R)-(+)-(**70**) (R)-(-)-(**61**)

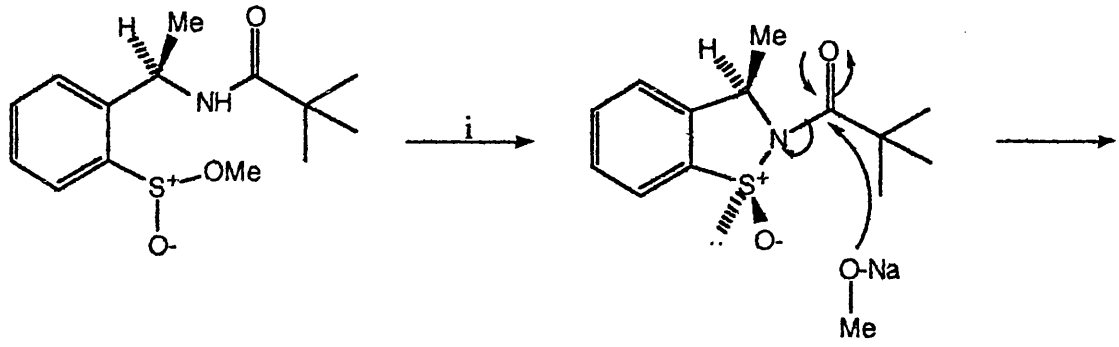
80%

i Potassium carbonate, n-bromosuccinimide, methanol, 2h, ii Aqueous sodium hydroxide (2 molar), tetrahydrofuran, 2h,

Scheme 121

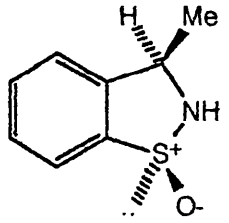
From the reported[81] synthesis of (**59**) treatment of sulphinyl chloride (**64**) with sodium hydride resulted in the formation of (**59**) as a single epimer. Ester (**145**) was treated with sodium hydride, but in place of expected ($S_{(S)}$ R)-(+)-*cis*-(**59**), ($S_{(S)}$ R)-(+)-*cis*-(**66**) was formed (Scheme 122) in 77% yield. From examination of the

spectroscopic data (**66**) was generated as a single stereoisomer. Formation of ($S_{(S)}$ R)-(+)-*cis*-(**59**) would be expected to occur first, followed by the removal of the trimethylacetyl group by the generated sodium methoxide.



(**145**)

($S_{(S)}$ R)-(+)-*cis*-(**59**)



($S_{(S)}$ R)-(+)-*cis*-(**66**)

77%

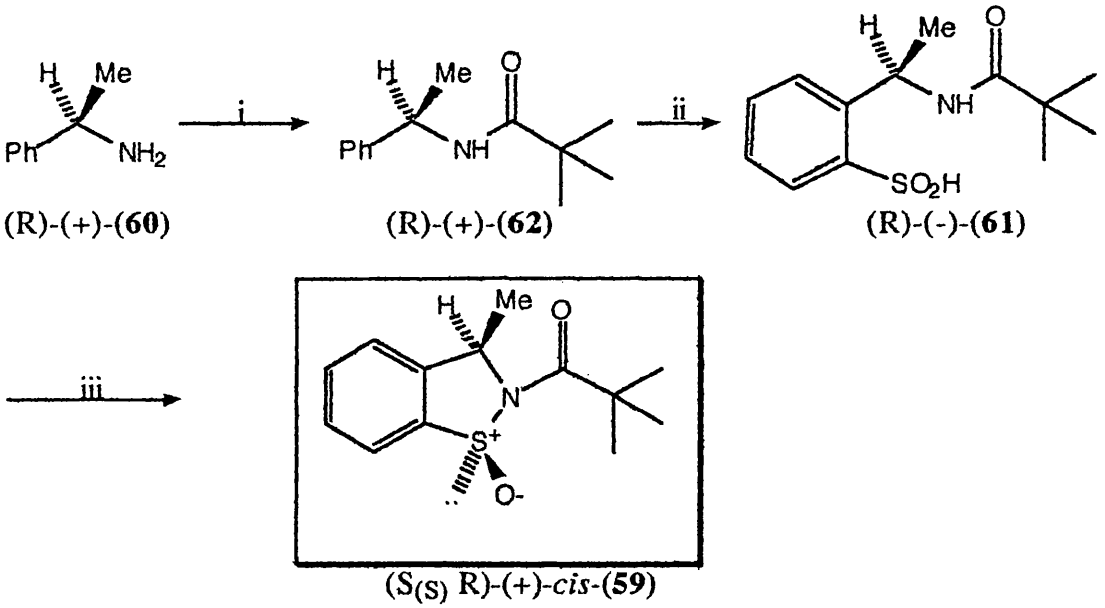
i Sodium hydride, tetrahydrofuran.

Scheme 122

3.0 CONCLUSION.

3.1 Synthesis of Cyclic Sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(59).

The required homochiral sulphoxide source ($S_{(S)}$ R)-(+)-*cis*-(**59**) has been synthesised as a single diastereoisomer in 54% yield from commercially available amine (R)-(+)-(**60**) in 3 steps (Scheme 123). The required cyclisation of sulphinyl chloride (**64**) to generate ($S_{(S)}$ R)-(+)-*cis*-(**59**) as a single diastereoisomer was achieved utilising 4-dimethylaminopyridine.[122]



(R)-(+)-(**60**) (R)-(+)-(**62**) (R)-(-)-(**61**)

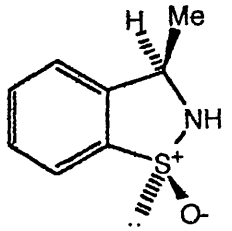
($S_{(S)}$ R)-(+)-*cis*-(**59**)

i Trimethylacetyl chloride, triethylamine, dichloromethane, ii *tert*-Butyllithium, diethyl ether; followed by sulphur dioxide, iii Thionyl chloride, 4-dimethylaminopyridine, tetrahydrofuran.

Scheme 123

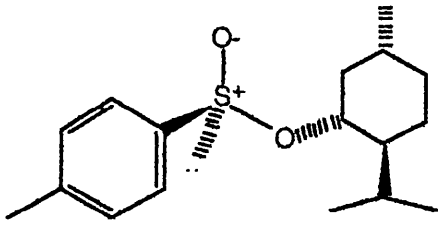
A possible mechanism has been forwarded to rationalise the selectivity exhibited by 4-dimethylaminopyridine in comparison to triethylamine and pyridine. The mechanism utilised the known highly nucleophilic nature of 4-dimethylaminopyridine and explained the differing selectivities exhibited by pyridine and triethylamine based on relative pK_a values. Two complementary reactions indicated that the ring closure was not an equilibrating process, but that the observed selectivity resulted from a non-reversible ring closure.

Sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) was isolated as a stable crystalline solid which showed no signs of decomposition after storage for six months. Nucleophilic attack occurred solely at the electrophilic sulphur for all the examples except sodium methoxide. The products of nucleophilic attack were isolated as single diastereoisomers (by ^{1}H NMR evaluation). The lack of coincident proton resonances for each diastereoisomer was confirmed by the synthesis of known diastereoisomeric mixtures. The sole exception to sulphur attack, sodium methoxide, resulted in reaction at the amide carbonyl with the subsequent removal of the trimethylacetyl group generating ($S_{(S)}$ R)-(+)-*cis*-(**66**) in 78% yield.



($S_{(S)}$ R)-(+)-*cis*-(**66**)

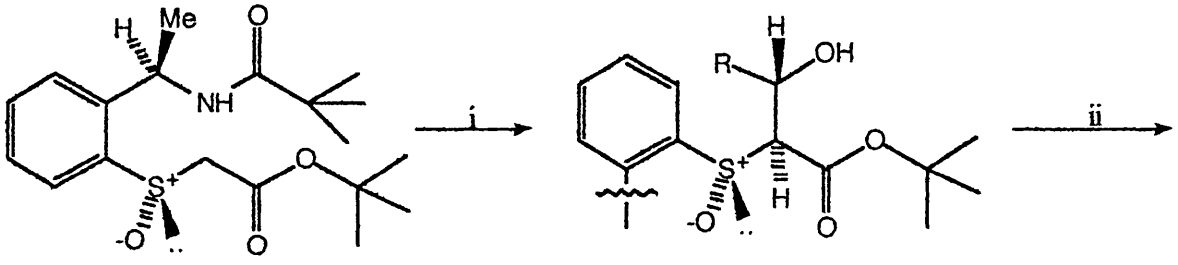
An advantage of utilising functionalised sulphoxides based on ($S_{(S)}$ R)-(+)-*cis*-(**59**) was the diastereoisomeric nature due to the fixed benzylic stereochemistry. These diastereoisomers were resolved in the ^{1}H NMR spectrum which allowed for ready assignment of reaction specificity. Sulphoxides generated from ($S_{(S)}$ R)-(+)-*cis*-(**59**) could be considered as containing an internal stereochemical marker, as opposed to the sulphoxides derived from (S)-(-)(**25**) which are enantiomeric and thus required complex ^{1}H NMR chiral shift reagent techniques to check stereochemical purity.



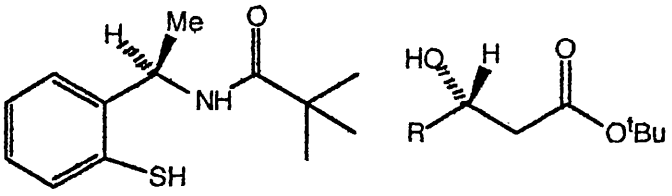
(S)-(-)-(**25**)

3.2 Aldol Chemistry.

With the synthesis of ($S_{(S)}$ R)-(+)-*cis*-(**59**) achieved, the resultant chemistry of the derived sulphoxides was investigated. The first area examined involved the reaction of the magnesium bromide enolate of sulphinyl acetate ($S_{(S)}$ R)-(-)-(**67**) with a series of aldehydes. Subsequent cleavage of adducts (**69**) with aluminium amalgam gave β-hydroxyesters (R)-(**71**) of high enantiomeric purity[123] (Scheme 124 and table 32). The isolation of the sulphur containing product, thiol (R)-(+)-(**70**), from the reductive cleavage was reported for the first time.



($S_{(S)}$ R)-(-)-(**67**) (**69**)

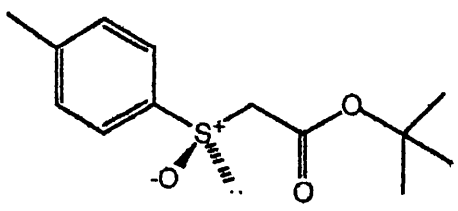


(R)-(+)-(**70**) (R)-(**71**)

i *tert*-Butyl magnesium bromide, RCHO, tetrahydrofuran, ii Aluminium amalgam, 10% aqueous tetrahydrofuran,

Scheme 124

The selectivity of the process paralleled that achieved with (S)-(**68**), suggesting that the amide side-chain had no detrimental effect on the observed stereospecificity.



(**68**)

Product (69).	R	Yield %	d.e.%
a	Ph	75	>92
b	4-Methoxyphenyl	70	>92
c	3-Methoxyphenyl	80	>92
d	2-Methoxyphenyl	90	33
e	4-Nitrophenyl	70	>92
f	2-Nitrophenyl	80	>92
g	*tert*-Butyl	90	>92
h	*iso*-Propyl	75	75
i	Methyl	60	50

The reaction of aldehydes with the magnesium bromide enolate of ($S_{(S)}$ R)-(-)-(67).

Table 32

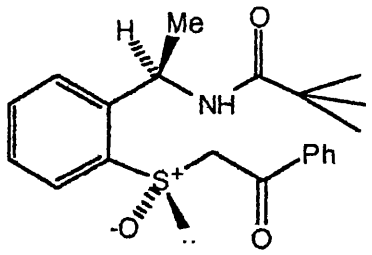
The sulphinyl acetate ($S_{(S)}$ R)-(-)-(**67**) was synthesised from ($S_{(S)}$ R)-(+)-*cis*-(**59**) in 87% yield as a single crystalline diastereoisomer. The single stereoisomer was subjected to a single crystal structure determination to confirm inversion of configuration at sulphur. The determined structure showed the required relative stereochemistry between the benzylic methyl and sulphoxide and since the stereochemistry of the benzylic position was fixed, the absolute configuration could be assigned. The crystalline nature of acetate ($S_{(S)}$ R)-(-)-(**67**) represented an advantage over acetate (S)-(**68**) since (S)-(**68**) existed as an oil which made further manipulations impractical. Adducts (**69**) were highly crystalline and adducts of poor diastereoisomeric excess could be recrystallised to give single diastereoisomers.

The selectivity exhibited in the reaction of ($S_{(S)}$ R)-(-)-(**67**) with the aldehydes was probed and shown to be due to a thermodynamic equilibration process *via* a highly chelated transition state. The equilibration result conflicted with the reported explanation for the selectivity of (**68**), which stated that the observed selectivity was

derived from kinetic control. The thermodynamic pathway for ($S_{(S)}$ R)-(-)-(**67**) allowed the reaction to be carried out at ambient temperature after initial deprotonation of ($S_{(S)}$ R)-(-)-(**67**) removing the practical difficulties involved in running reactions at a constant temperature of -78°C.

3.3 Synthesis of β-Ketosulphoxides.

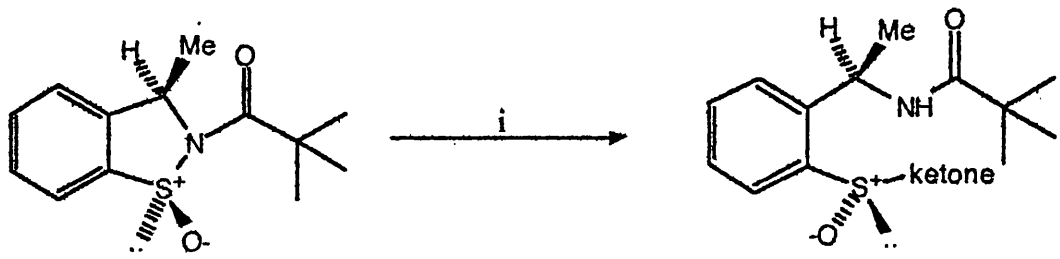
A single one step procedure was sought to generate these synthetically useful compounds from ($S_{(S)}$ R)-(+)-*cis*-(**59**) and ketone enolates. Acetophenone was deprotonated by a trio of bases in three different solvents and the resultant reaction of the ketone enolate with ($S_{(S)}$ R)-(+)-*cis*-(**59**) investigated. The result of this study showed the sodium enolate of acetophenone (derived *via* deprotonation with sodium bis-(trimethylsilyl)amide) in toluene reacted with ($S_{(S)}$ R)-(+)-*cis*-(**59**) gave β-ketosulphoxide ($S_{(S)}$ R)-(-)-(**85**) in 78% yield as a single diastereoisomer.



($S_{(S)}$ R)-(-)-(**85**)

This new methodology represented a great advantage over the synthesis of β-ketosulphoxides derived from (S)-(-)-(**25**) since a two step procedure was required to generate the (S)-(-)-(**25**) derived β-ketosulphoxides.

The scope of the reaction between the sodium ketone enolate and (**59**) was successfully extended to a range of other ketones and a single example of a lactone (Scheme 125 and table 33).



($S_{(S)}$ R)-(+)-*cis*-(**59**)

i Sodium enolate of ketone, toluene, -78°C-ambient temperature.

Scheme 125

Ketone	Yield %
Acetophenone	78
4-Methoxyacetophenone	quantitative
2-Methylacetophenone	73
Pinacolone	70
Propiophenone	75[a]
Butyrolactone	76[a]
Cyclopentanone	45[a]
Cyclohexanone	78
Cycloheptanone	98[a]
Cyclodecanone	88[a]
Cyclopentadecanone	76[a]

a. Mixture of epimers at C-2

Synthesis of β-ketosulphoxides from ($S_{(S)}$ R)-(+)-*cis*-(59).

Table 33

3.4 Reduction Of The β-Ketosulphoxides.

With a ready synthesis of β-ketosulphoxides achieved, their reduction chemistry was investigated. Reduction of β-ketosulphoxide ($S_{(S)}$ R)-(-)-(**85**) with a variety of

reducing agents exhibited the same trends observed within the β-ketosulphoxides derived from (S)-(-)-(**25**). The best results were achieved utilising the complementary DIBAL-H and DIBAL-H zinc (II) bromide reduction protocols with the observed selectivities comparable with those reported by other workers for (S)-(-)-(**25**) derived β-ketosulphoxides. The reduction protocol was successfully extended to the other C-2 unsubstituted β-ketosulphoxides (table 34). The β-hydroxysulphoxides generated were all highly crystalline and low diastereoisomeric ratios could easily be converted to diastereoisomeric purity by recrystallisation.

trans *cis*

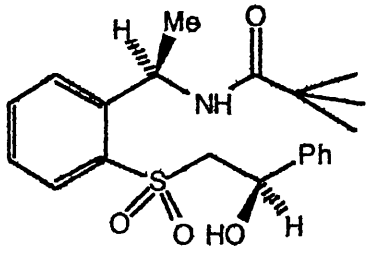
i Reducing agent, tetrahydrofuran, -78°C.

R	Reducing agent	*trans*	*cis*	Yield %
Phenyl	DIBAL-H	94	6	73
"	DIBAL-H $ZnBr_2$	<2	>98	80
4-Methoxyphenyl	DIBAL-H	91	9	90
"	DIBAL-H $ZnBr_2$	<2	>98	100
2-Methylphenyl	DIBAL-H	91	9	90
"	DIBAL-H $ZnBr_2$	<2	>98	90

Reduction of β-ketosulphoxides

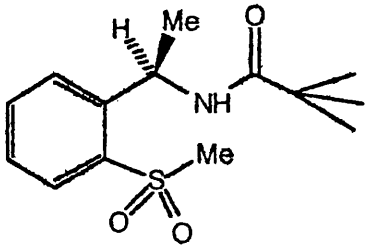
Table 34

The removal of the sulphinyl unit from the β-hydroxysulphoxides proved to be problematic. Initial studies were targeted towards the selective oxidation of β-hydroxysulphoxide ($S_{(S)}$ R, S)-(-)-(**96**) to β-hydroxysulphone (R, S)-(**107**) with subsequent deprotonation of the alcohol followed by expulsion of the sulphone which would generate homochiral styrene oxides.



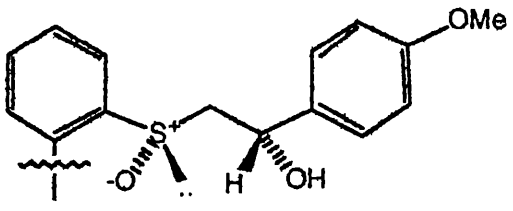
(R, S)-(**107**)

The deprotonated β-hydroxysulphones underwent a retro-aldol reaction which gave methyl sulphone (R)-(**109**).

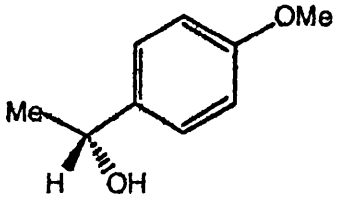


(R)-(**109**)

With the known instability of the amide to Pummerer conditions, Raney™ nickel reductive cleavage was subsequently examined. Initial results appeared promising with the diastereoisomerically pure β-hydroxysulphoxides undergoing cleavage to give the required secondary alcohol and amide (R)-(+)-(**62**). The total loss of the sulphur atom was disappointing, since no oxidative regeneration to the acid (R)-(-)-(**61**) was possible. A more important problem associated with the usage of Raney™ nickel was the secondary alcohols formed had partially racemised. Reductive cleavage of diastereomerically pure ($S_{(S)}$ R, R)-(-)-(**100**) gave secondary alcohol (R)-(**110**) with an enantiomeric excess (as determined by conversion to the (R)-(+)-MTPA ester) of only 81%.



($S_{(S)}$ R, R)-(-)-(**100**)

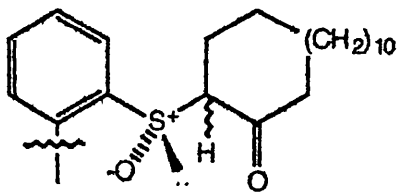


(R)-(**110**)

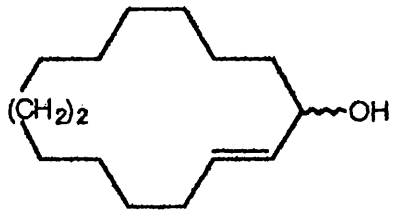
Examination of the reductive cleavage of the other *cis*-β-hydroxysulphoxide yielded secondary alcohols with low enantiomeric excesses. The alcohols formed were enriched in the (R)-isomer as expected from the cleavage of the *cis*-β-hydroxysulphoxide. A possible mechanism involving an oxidation reduction sequence has been forwarded as a rationale for these poor results.

3.5 Chemistry of the Cyclic β-Ketosulphoxides.

From work carried out within the group and examination of the literature a means for synthesising enantiomerically enriched allylic alcohols from the cyclic β-ketosulphoxides was examined. The cyclopentadecanone derived cyclic β-ketosulphoxide ($S_{(S)}$ R)-(**95**) was treated with a trio of reducing reagents and then heated in toluene at 60°C to generate allylic alcohol (**120**) in varying enantiomeric purity as determined by conversion to the (R)-(+)-MTPA ester and ^1H NMR thereof (table 35).



($S_{(S)}$ R)-(**95**)



(**120**)

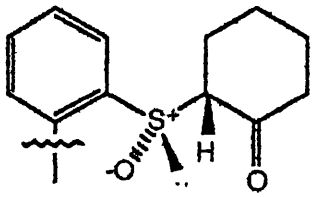
Reducing agent	Enantiomeric purity %
Sodium borohydride	< 5
DIBAL-H	12
DIBAL-H/zinc (II) bromide	88[a]

a. Opposite enantiomer formed wrt the DIBAL-H reaction.

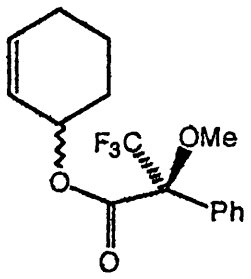
Reduction of ($S_{(S)}$ R)-(95) to form allylic alcohol (120).

Table 35.

The above methodology was extended to the cyclohexanone derived β-ketosulphoxide ($S_{(S)}$ R)-(-)-(**92**). The thermal elimination proved to be difficult on the formed β-hydroxysulphoxide but acylation to give the Mosher ester followed by heating in refluxing toluene, resulted in the formation of (**130**) with varying degrees of stereochemical purity.



($S_{(S)}$ R)-(-)-(**92**)



(**130**)

Reducing agent	Enantiomeric purity %
DIBAL-H	>95
DIBAL-H/zinc (II) bromide	< 5

Synthesis of allylic ester (130).

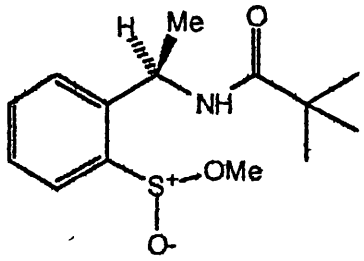
Table 36

The sulphur containing compounds from the thermal eliminations were converted into thiol (R)-(+)-(**70**) by utilising triphenylphosphine-iodine reduction methodology.

3.6 Regeneration of Sulphoxide Source ($S_{(S)}$ R)-(+)-*cis*-(59)

Thiol (R)-(+)-(**70**) had been recovered as the sulphur containing moiety from both the aldol and elimination chemistry, hence a method for the oxidation of (R)-(+)-(**70**) to the sulphinic acid oxidation level was required. Model studies identified the use of sodium periodate (2 equivalents) in aqueous methanol as a means for performing this transformation. To circumvent the sole formation of disulphide (**73**) the reaction was carried out in refluxing solvent. The crude reaction mixture from this reaction,

containing epimeric (**145**) and (**59**) was treated with aqueous sodium hydroxide to generate the required acid (R)-(-)-(**61**) in 82% yield.



(**145**)

This required transformation was also achieved utilising a two step procedure involving oxidation with n-bromosuccinamide and methanol to (**145**) followed by saponification to (R)-(-)-(**61**).

3.7 Final Comments

The readily synthesised sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) has been shown to control asymmetric processes to a high degree. The sulphur containing portion recovered after removal of the auxiliary has been successfully converted back to ($S_{(S)}$ R)-(+)-*cis*-(**59**). Sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(**59**) has the advantage of a built-in stereochemical marker (the benzylic methyl) to facilitate assignment of stereochemical purity. The product crystallinity of ($S_{(S)}$ R)-(+)-*cis*-(**59**) derived sulphoxides aided practical usage, and enabled enrichment of poorly selective reactions by recrystallisation. The reaction of sodium ketone enolates with ($S_{(S)}$ R)-(+)-*cis*-(**59**) represented a significant advantage over conventional β-ketosulphoxide synthesis.

Therefore, a practically useful recyclable source of homochiral sulphoxide has been introduced for asymmetric synthesis.

4.0. EXPERIMENTAL

4.1 General Details.

All melting point measurements were carried out on a Gallenkamp hot stage apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1310 grating Spectrometer. ^{1}H-NMR were recorded on either a Jeol GX270 FT at 270 MHz or a Jeol EX400 instrument operating at 400MHz. The observed spectra were for solutions in deuteriochloroform unless otherwise stated. The chemical shifts were recorded relative to tetramethylsilane as an internal standard; all coupling constants, *J*, are reported in Hz. ^{13}C NMR spectra were recorded on a Jeol GX270 FT instrument operating at 67.8 MHz or a Jeol EX400 instrument operating at 100MHz. The spectra were recorded for solutions in deuteriochloroform unless otherwise stated. The chemical shifts were recorded relative to deuteriochloroform as internal standard in a broad band decoupled mode; the multiplicities were obtained by using 135 and 90 DEPT experiments to aid in assignments (q, methyl; t, methylene; d, methine; s, quaternary).

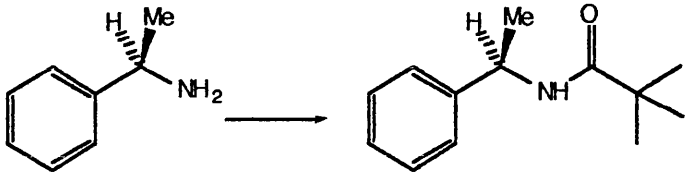
Mass spectra were recorded on a VG analytical 7070E instrument with VG2000 data system using electron ionisation (E.I., 70eV), chemical ionisation (C.I. isobutane) and fast atom bombardment (F.A.B.) techniques. High resolution MS was carried out by the S.E.R.C. regional service at the University College of Swansea. Microanalytic data were obtained on a Carlo Erba 1106 Elemental Analyser. Optical rotations were carried out using a Perkin Elmer 141 polarimeter.

Flash chromatography[124] was performed on Merck silica gel 60 and the solvents ethyl acetate, acetone and petroleum ether (boiling range 60-80°C) distilled before use. All reactions were monitored by TLC on aluminium or plastic sheets precoated with 250μM silica gel which were visualised by UV light and then by potassium permanganate solution, phosphomolybdic acid solution or anisaldehyde solution.

Tetrahydrofuran and diethyl ether were dried over sodium benzophenone ketyl under nitrogen and distilled prior to use. Toluene was dried over sodium and distilled before use. Dichloromethane was distilled from phosphorus pentoxide. 4-Dimethylaminopyridine (DMAP) was provided in the form of a gift from Reilly chemicals (USA) or purchased from the Aldrich Chemical Company. *n*-Butyllithium and *t*-butyllithium were provided as solutions in hexane of 1.6 and 1.7M respectively. Methyllithium was provided as a 1.4M solution in diethyl ether. Diisobutylaluminium hydride and sodium bis-(trimethylsilyl)amide were provided as 1.0M solutions in hexanes and tetrahydrofuran respectively. All reagents were purified[125] before use. All reactions, unless otherwise stated, were carried out in Schlenk glassware under a positive pressure of dry nitrogen in a vacuum flame dried apparatus.

4.2 Synthesis Of Cyclic Sulphinamide ($S_{(S)}$ R)-(+)-*cis*-(59)

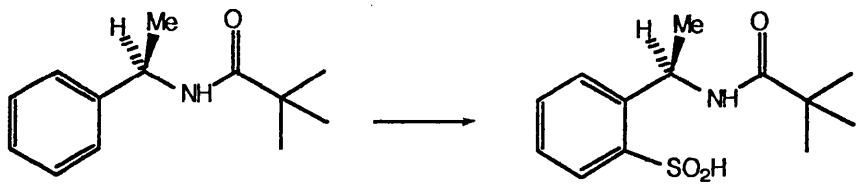
4.2.1 Synthesis of sulphinic acid (R)-(-)-(61)



(R)-(+)-(**60**) (R)-(+)-(**62**)

Trimethylacetyl chloride (43.0 cm^3, 350 mmol) was added dropwise to a cooled (O°C), mechanically stirred, solution of (R)-(+)-(**60**) (37.8g, 40.0 cm^3, 315 mmol) and triethylamine (48.5 cm^3, 350 mmol) in dichloromethane (750cm^3). The resulting white suspension was stirred at ambient temperature for 16 hrs before water (250cm^3) was added and the two resultant layers separated. The aqueous portion was extracted with dichloromethane (2 x 50cm^3). The combined organic fractions were washed with dilute hydrochloric acid (2M, 200 cm^3), dried over anhydrous sodium sulphate and the solvent was removed at reduced pressure to yield a white solid from which (R)-(+)-(**62**) was isolated by recrystallisation from dichloromethane-hexane (51.5g, 80%).

m. p. 125°C; $[\alpha]_D^{20}$= +102.4° (c=0.63, chloroform); υ_{max} (nujol mull/cm^{-1}); 3337, 1637; δ_H 1.19 (9H, s, CMe_3), 1.46 (3H, d, *J* 7.0, $CHCH_3$), 5.10 (1H, quintet, *J* 7.0, C*H*), 5.92 (1H, bd, *J* 7.0, N*H*), 7.24-7.35 (4H, m, aromatic *H*); δ_C 21.63 (q), 27.41 (q), 38.18 (s), 48.33 (d), 125.5 (d, 2C), 127.7 (d), 128.2 (d, 2C), 143.6 (s), 177.3 (s); *m/z* 206 ($M+1^+$), 105 (95); [found: C, 76.5; H 9.1; N, 7.1, $C_{13}H_{19}NO$ requires C, 76.09; H, 9.27; N, 6.83 %].



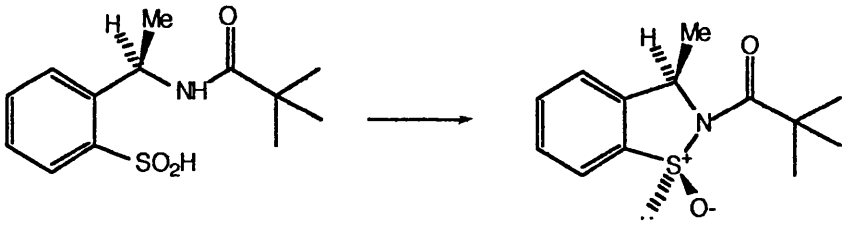
(R)-(+)-(**62**) (R)-(-)-(**61**)

To a mechanically stirred solution of (R)-(+)-(**62**) (2.50g, 12.25 mmol) in diethyl ether at -78°C was added rapidly a solution of *tert*-butyllithium (7.20 cm^3, 12.25

mmol). After the resultant white suspension had been stirred at -78°C for 0.5 hr a further portion of *tert*-butyllithium (8.65 cm^3, 14.70 mmol) was added over 0.5 hr. The solution was stirred at -78°C for 0.5 hr then allowed to warm up to 0°C at which temperature it was stirred for 0.5 hr. The resulting thick red suspension was recooled to -78°C and a stream of sulphur dioxide gas was passed over the surface of the liquid until all of the red colouration had faded, to be replaced by a white suspension. The suspension was allowed up to ambient temperature and quenched by the addition of water (20 cm^3). Solid sodium hydroxide was added until the pH of the solution exceeded 12 and the resulting layers were separated. The aqueous layer was extracted with further dilute sodium hydroxide (2M, 50 cm^3). The basic aqueous extracts were combined and treated with concentrated hydrochloric acid until the pH was below 1, at which point a white suspension had formed. The suspension was extracted with dichloromethane (5 x 50 cm^3), the combined organic extracts were dried over anhydrous sodium sulphate and the filtrate was evaporated at low pressure to give sulphinic acid R-(-)-(**61**) (3.12 g, 11.6 mmol, 95%).

m. p. 66°C; $[\alpha]_D^{20}$= -70° (c=0.43, chloroform); υ_{max} (nujol mull)/cm^{-1} 3316, 2485, 1660, 1102, 805; δ_H 1.16 (9H, s, CMe_3), 1.55 (3H, d, *J* 6.8, $CHCH_3$), 6.10 (1H, quintet, *J* 6.8, C*H*), 6.53 (1H, bd, *J* 6.8, N*H*), 7.49 (3H, m, aromatic *H*), 7.61 (1H, d, *J* 6.4, aromatic *H*); δ_C 22.21 (q), 27.37 (q), 37.95 (s), 43.98 (d), 122.3 (d), 126.0 (d), 127.2 (d), 131.7 (d), 141.1 (s), 145.2 (s) 176.9 (s); *m/z* 270 (10, $M+1^+$ 100), 252 (7), 205 (21) and 150 (93) [*m/z*, found 270.1160; $C_{13}H_{19}NO_3S$ requires ($M+1^+$) 270.1164].

4.2.2 Cyclisation of the sulphinic acid



(R)-(-)-(**61**) ($S_{(S)}$ R)-(+)-*cis*-(**59**)

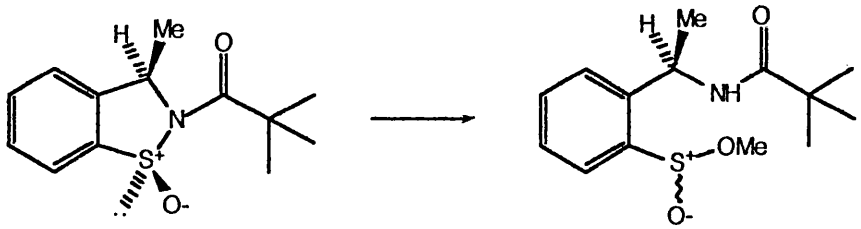
Thionyl chloride (2.50cm^3, 34.27mmol) was added dropwise with stirring to a cooled (0°C) solution of (R)-(-)-(**61**) (5.00g, 18.59 mmol) and 4-DMAP (2.43g, 19.92 mmol) in THF (50cm^3) under nitrogen. The mixture was stirred at room temperature for 16 h. Further 4-DMAP (5.00g, 40.98 mmol) was added portionwise and the mixture stirred at room temperature for a further 2 hours. After this time the reaction was quenched by the addition of saturated aqueous ammonium chloride (50cm^3), the organic phase was separated and the aqueous solution extracted with ethyl acetate (3 x 50cm^3). The combined organic phases were washed with brine (50cm^3), dried (sodium sulphate) and the solvent removed to give a yellow oil which solidified on standing. ($S_{(S)}$R)-(+)-*cis*-(**59**) was isolated by flash chromatography (9:1 petrol (60/80)/EtOAc) as a white solid which was recrystallised from dichloromethane/hexane (3.13g, 12.5 mmol, 67%).

m.p. 115-117°C; $[\alpha]_D^{20}$=+9.00° (c=0.8, ethanol); υ_{max} (nujol mull)/cm^{-1} 1661, 1278, 1137, 1096; δ_H 1.19 (9H, s, CMe_3), 1.74 (3H, d, *J* 6.8, $CHCH_3$), 5.64 (1H, q, *J* 6.8, C*H*), 7.44-7.62 (3H, m, aromatic *H*), 7.77 (1H, d, *J* 6.7, aromatic *H*); δ_C 23.94 (q), 28.48 (q), 41.03 (s), 63.96 (d), 123.6 (d), 124.8 (d), 128.8 (d), 132.4 (d), 143.0 (s, 2C), 177.0 (s); *m/z* 149 (23), 91 (26), and 57 (100) [found: C, 59.3; H, 6.5; N 5.3%; $C_{13}H_{17}NO_2S$ requires C, 59.6; H, 6.5; N, 5.3%]. The aqueous extract from the above reaction was acidified with concentrated HCl until the pH was below 1 and extracted with dichloromethane (3 x 50cm^3) to obtain a quantity of unreacted R-(-)-(**61**) which was retained for use in subsequent reactions.

Formation of a quantity of the (R(S)R)-*trans*-(**59**) was observed in the case where triethylamine or pyridine was used as a base in place of DMAP; (R(S)R)-*trans*-(**59**)

δ_H 1.50 (9H, s, $COCMe_3$), 1.56 (3H, d, *J* 6.8, $CHCH_3$), 5.80 (1H, q, *J* 6.8, $CHCH_3$).

4.3 Nucleophilic Ring Opening Of ($S_{(S)}$ R)-(+)-*cis*-(59) With Simple Nucleophiles

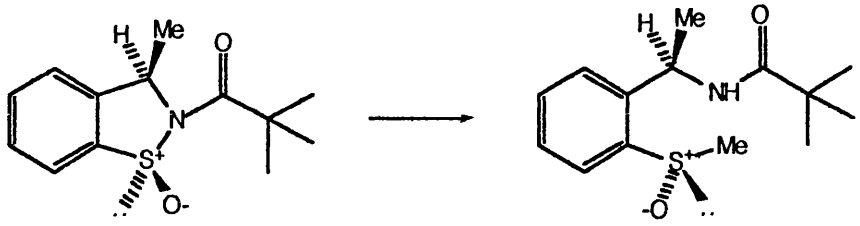


($S_{(S)}$ R)-(+)-*cis*-(**59**) (**145**)

n-Butyllithium (1.50cm^3, 2.40 mmol) was added dropwise to cooled (O°C) methanol (1.00cm^3, 24.7 mmol) under a nitrogen atmosphere. After stirring for one hour a solution of ($S_{(S)}$R)-(+)-*cis*-(**59**) (0.249g, 1.00 mmol) in THF (1cm^3) was added dropwise. Examination by tlc showed full consumption of starting material within one hour. The reaction was then quenched with saturated aqueous ammonium chloride (5cm^3) and extracted with ethyl acetate (3 x 5cm^3). The combined organics were dried over anhydrous sodium sulphate and the filtrate evaporated to to give sulphinate ester (**145**) as a 2:1 mixture of diastereoisomers (0.180g, 64%);

υ_{max} (nujol mull)/cm^{-1} 3352 (NH), 1649 (C=O), 1112 (SO_2Me); δ_H 1.18 (6H, s, CMe_3, major isomer), 1.22 (3H, s, CMe_3, minor isomer), 1.48 (2H, d, *J* 7.0, CH_3, major isomer), 1.51 (1H, d, *J* 7.0, CH_3, minor isomer), 3.55 (2H, s, OCH_3 major isomer), 3.57 (1H, s, OCH_3 minor isomer), 5.38 (0.66H, quintet, *J* 7.0, *CH* major isomer), 5.46 (0.33H, d, *J* 7.0, *CH* minor isomer), 5.92 (0.33H, bd, *J* 7.0, N*H*, minor isomer), 6.02 (0.66H, bd, *J* 7.0, N*H*, major isomer), 7.26-7.57 (3H, m, aromatic *H*, both isomers), 7.97 (1H, d, *J* 1.65, aromatic *H*, minor isomer), 8.00 (1H, d, *J* 1.65, aromatic *H*, major isomer); δ_C Major isomer 21.48 (q), 27.15 (q), 38.15 (q), 44.28 (s), 49.95 (d), 124.1 (d), 125.8 (d), 127.1 (d), 132.4 (d), 140.4 (s), 143.3 (s), 177.4 (s); minor isomer; 22.45 (q), 27.25 (q), 38.28 (q), 44.09 (s), 50.44

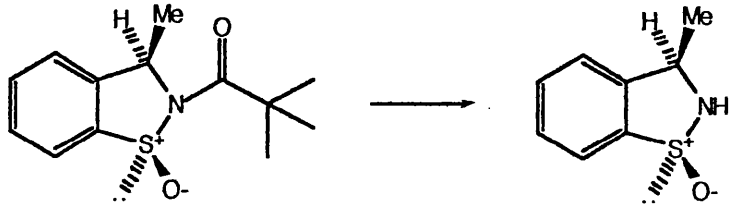
(d), 124.7 (d), 125.4 (d), 127.3 (d), 132.5 (d), 139.9 (s), 143.0 (s), 177.2 (s) ; *m/z* (CI) 284 (100,M+1$^+$), 252 (14), 204 (17), 150 (60).



($S_{(S)}$ R)-(+)-*cis*-(**59**) ($S_{(S)}$ R)-(-)-(**82**)

Methyllithium (0.30cm^3, 0.42mmol) was added dropwise to a solution of ($S_{(S)}$R)-(+)-*cis*-(**59**) (0.10g, 0.40mmol) in diethyl ether (7cm^3) at -78°C. The reaction was stirred at this temperature for 1 hr and then quenched by the addition of saturated ammonium chloride solution (7cm^3). The organic phase was separated and the aqueous layer was extracted with dichloromethane (3 x 10cm^3). The combined organic extracts were washed with brine, dried over sodium sulphate and the solvent removed under reduced pressure to yield an oil from which ($S_{(S)}$ R)-(-)-(**82**) was isolated by flash chromatography (50/50 petroleum ether/ethyl acetate) and recrystallisation from petroleum ether/ethyl acetate (96 mg, 89%).

m.p.118°C; $[\alpha]_D^{25}$=-100° (c=0.75, chloroform); υ_{max} (nujol mull)/cm^{-1} 3410, 1640, 1060; δ_H 1.11 (9H, s, CMe3), 1.43 (3H, d, *J* 7.0, CHC*H*3), 2.70 (3H, s, SOC*H*3), 5.23 (1H, quintet, *J* 7.0, C*H*), 6.20 (1H, bd, *J* 7.0, N*H*), 7.38-7.43 (3H, m, aromatic *H*), 7.85 (1H, m, aromatic *H*); δ_C 21.7 (q), 27.2 (q), 38.3 (s), 43.0 (q), 45.0 (d),123.9 (d), 126.2 (d), 128.5 (d), 131.3 (d), 141 (s), 143 (s) 177 (s); m/z 268 (M+1, 100), 234 (10), 204 (16) [found: C, 62.4; H, 8.06; N 5.25%; $C_{13}H_{19}NO_3S$ requires C, 62.4; H, 7.94; N, 5.24%].



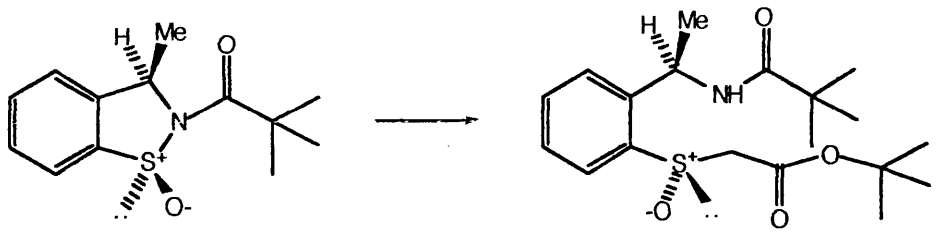
($S_{(S)}$ R)-(+)-*cis*-(**59**) ($S_{(S)}$ R)-(+)-*cis*-(**66**)

To a stirred solution of methanol (0.082cm^3, 2.00mmol) in tetrahydrofuran (1cm^3) was added in a single portion sodium hydride (60% dispersion in mineral oil, 0.044g, 1.10mmol). The resultant reaction mixture was stirred at ambient temperature for 1h, cooled to 0°C and a solution of the ($S_{(S)}$R)-(+)-*cis*-(**59**) (0.250g, 1.00mmol) in tetrahydrofuran (2cm^3) added dropwise. The reaction was stirred at ambient temperature for 0.5h and then saturated aqueous ammonium chloride (3cm^3) was added. The reaction mixture was extracted with ethyl acetate (3x5cm^3), the combined organic phases dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure to yield ($S_{(S)}$ R)-(+)-*cis*-(**66**) as off-white crystalline solid (0.132g, 79%).

m.p.140°C (ethyl acetate hexane); $[\alpha]_D^{25}$=-28.6° (c=0.1.52, methanol); υ_{max} (nujol mull)/cm^{-1} 1278, 1137, 1096; δ_H 1.68 (3H, d, *J* 6.78, CH*Me*), 4.87 (1H, quintet, *J* 6.78, C*H*Me), 5.23 (1H, bs, NH), 7.39-7.58 (3H, m, aromatics), 7.78 (1H, d, *J* 6.78, aromatic); δ_C 25.80 (q), 62.52 (d), 123.3 (d), 124.5 (d), 128.6 (d), 131.3 (d), 143.6 (s), 145.2 (s) ; m/z 168 (M+1, 100), 150 (10) [found: C, 57.5; H, 5.51; N 8.26%; C_8H_9NOS requires C, 57.5; H, 5.39; N, 8.38%].

4.4 Aldol Chemistry

4.4.1 Synthesis of sulphinylacetate ($S_{(S)}$ R)-(-)-(**67**)



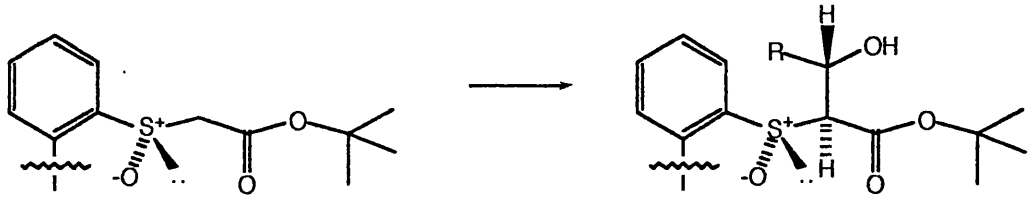
($S_{(S)}$ R)-(+)-*cis*-(**59**) ($S_{(S)}$ R)-(-)-(**67**)

Bromoethane (3.56cm^3, 47.7mmol) was added dropwise to a stirred suspension of magnesium (1.15g, 42.48mmol) in diethyl ether (70cm^3) and the mixture was stirred at ambient temperature until all the magnesium had been consumed. Di-isopropylamine (5.53cm^3, 39.46mmol) was added dropwise and the reaction mixture was heated at reflux for 1 hr. The resultant red suspension was cooled to -40°C and tetrahydrofuran (5cm^3) added. A solution of *tert*-butyl acetate (4.22 cm^3, 40.15 mmol) and ($S_{(S)}$ R)-(+)-*cis*-(**59**) (3.22g, 12.81 mmol) in tetrahydrofuran (5cm^3) and diethyl ether (40cm^3) was added dropwise over one hr. The reaction was stirred for 4 hr at -40°C before saturated ammonium chloride solution (50cm^3) was added and the organic phase separated. The aqueous phase was extracted with ethyl acetate (3 x 50cm^3) and the combined organic extracts were washed with brine (25 cm^3), dried over sodium sulphate. Removal of the solvent followed by flash chromatography (50/50 ethyl acetate/petroleum ether) gave ($S_{(S)}$R)-(-)-(**67**) as a white solid which was recrystallised from dichloromethane/hexane (3.85g, 84%).

m.p. 118-119°C; $[\alpha]_D^{20}$= -114.2° (c=0.33, chloroform); υ_{max} (nujol mull)/cm^{-1} 3350 (CO), 3000, 1730 (CO_2), 1650 (CON), 1040 (SO); δ_H 1.18 (9H, s, CMe_3), 1.39 (9H, s, CMe_3), 1.53 (3H, d, *J* 7.0, CH_3), 3.74 (1H, d, *J* 13.6, CH_2), 3.90 (1H, d, *J* 13.6, CH_2), 5.34 (1H, quintet, *J* 7.0, *CH*Me), 6.25 (1H, bd, *J* 7.0, NH), 7.50-7.47 (3H, m, Aromatic *H*), 7.93 (1H, d, *J* 5.9, aromatic H); δ_C 21.57 (q), 27.24 (q), 27.67 (q), 38.27 (s), 45.60 (d), 60.65 (t), 82.84 (s), 125.2 (d), 126.5 (d),

(d), 128.2 (d), 131.8 (d), 141.0 (s), 142.0 (s), 163.8 (s), 177.0 (s); *m/z* (EI) 368 (9, $M+1^+$), 312 (100) [found: C, 61.90 ; H, 7.96; N 3.76%; $C_{19}H_{29}NO_4S$ requires C, 62.10; H, 7.96; N, 3.76%].

4.4.2 Reaction of ($S_{(S)}$ R)-(-)-(**67**) with aldehydes



($S_{(S)}$ R)-(-)-(**67**) **(69a-i)**

tert-Butyl bromide (1.54g, 7.92 mmol) was added dropwise to a cooled (O°C) stirred suspension of magnesium (0.190g, 7.92 mmol) in diethyl ether ($3cm^3$). The mixture was stirred until all the magnesium had been consumed at which point the resultant grey-brown solution was added dropwise at to a stirred solution of sulphinyl ester ($S_{(S)}$ R)-(-)-(**67**) (0.139g, 0.38 mmol) in THF (20 cm^3) at -78°C. The white suspension was stirred for 1.5 hrs at -78°C before a solution of the aldehyde (1.14 mmol) in THF (5 cm^3) was added dropwise to the solution, which was stirred at -78°C for 4 hrs and then allowed up to ambient temperature over a period of ca. 16 hrs (left in cardice bath overnight). Saturated ammonium chloride solution (25 cm^3) was added and the organic phase removed. The aqueous phase was extracted with ethyl acetate (3 x 25 cm^3) and the organic phases were combined, washed with brine and dried over sodium sulphate. Removal of solvent and flash chromatography furnished the aldol products **(69a-i)**

Adduct with benzaldehyde, (**69a**).- The product was isolated as a white foam which was recrystallised from dichloromethane-hexane to yield (**69a**) as a colourless crystalline solid (77%).

m.p. 184°C; $[\alpha]_D^{25}$= -158.7° (c=0.126, chloroform); υ_{max} (nujol mull)/cm^{-1} 3320, 1720, 162 and 1040; δ_H 1.13 (9H, s, OCMe3), 1.14 (9H, s, CMe3), 1.51 (d, *J* 6.8,

C*H*3), 4.21 (1H, d, *J* 5.1, SOC*H*), 5.18 (1H, bd, PhC*H*), 5.24 (1H, quintet, *J* 6.8, C*H*Me), 5.89 (1H, bd, *J* 6.8, NH), 7.24-8.00 (9H, m, aromatic *H*); δ_C 21.18 (q), 27.37 (q), 27.57 (q), 38.37 (s), 44.70 (d), 72.10 (d), 72.36 (d), 83.10 (s), 126.0 (s), 126.2 (d, 2C), 126.4 (d), 128.0 (d),128.3 (d), 128.4 (d, 2C), 131.8 (d), 139.5 (s), 139.7 (s), 142.3 (s) 165.5 (s), 177.3 (s); *m/z* (FAB) 474 (32, M+1$^+$), 418 (M-tBu$^+$ 74), 312 (M-tBu-PhCHO$^+$, 10) [found: C, 65.60; H, 7.45; N 2.91%; $C_{26}H_{35}NO_5S$ requires C, 65.96; H, 7.40; N, 2.96%;].

Adduct with 4-methoxybenzaldehyde (**69b**).- The product was initially isolated as a white foam which was recrystallised from ether to yield (**69b**) as a colourless crystalline solid (70%).

m.p. 112-114°C; $[\alpha]_D^{25}$= -125° (c=0.088, chloroform); υ_{max} (nujol mull)/cm^{-1} 3400, 3200, 1730, 1660 and 1040; δ_H 1.06 (9H, s, OCMe3), 1.08 (9H, s, CMe3), 1.44 (d, *J* 6.8, C*H*3), 3.80 (3H, s, OC*H*3), 4.07 (1H, d, *J* 5.5, C*H*CO), 5.16 (1H, bd, C*H*OH), 5.16 (1H, quintet, *J* 6.8, C*H*Me), 5.76 (1H, bd, *J* 6.8, NH), 6.81 (2H, d, *J* 8.6, aromatic *H*), 7.20-7.43 (4H, m, aromatic *H*), 7.89 (2H, m, aromatic *H*); δ_C 21.15 (q), 27.41 (q), 27.63 (q), 38.40 (s), 44.73 (d), 55.24 (q), 72.00 (d), 72.14 (d), 83.00 (s), 113.9 (d), 125.9 (d), 126.5 (d), 127.7 (d, 2C), 128.3 (d), 131.7 (d), 139.0 (s), 140.0 (s), 142.0 (s) 159.0 (s), 165.4 (s), 177.3 (s); *m/z* (FAB) 504 (89, M+1$^+$), 448 (M-tBu$^+$, 57), 312 (M-tBu-(MeO)C_6H_4CHO$^+$ 50); [found: C, 64.00; H, 7.40; N 2.80%; $C_{26}H_{35}NO_6S$ requires C, 64.39; H, 7.40; N, 2.78%;].

Adduct with 3-methoxybenzaldehyde (**69c**).- The product was initially isolated as a yellow foam which was recrystallised from ether to yield (**69c**) as a colourless crystalline solid (80%).

m.p. 66-68°C; $[\alpha]_D^{25}$= -169° (c=0.14, chloroform); υ_{max} (nujol mull)/cm^{-1} 3400, 3200, 1730, 1660 and 1040; δ_H 1.11 (9H, s, OCMe3), 1.15 (9H, s, CMe3), 1.49 (d, *J* 6.8, C*H*3), 3.77 (3H, s, OC*H*3), 4.30 (1H, d, *J* 7.50, SOC*H*), 5.12 (1H, bd, *J* 6.8, C*H*OH), 5.25 (1H, quintet, *J* 6.8, C*H*Me), 5.94 (1H, bd, *J* 6.8, NH), 6.78-7.90 (8H,

m, aromatic *H*); δ_C 21.34 (q), 27.34 (q), 27.60 (q), 38.40 (s), 44.76 (d), 55.20 (q) 72.14 (d), 72.23 (d), 83.10 (s), 111.2 (d), 114.2 (d), 118.4 (d), 125.9 (d) 126.6 (d), 128.1 (d), 129.4(d), 131.8 (d), 139.0 (s), 141.3 (s), 142.6 (s), 159.6 (s), 165.6 (s), 177.3 (s); *m/z* (FAB) 504 (36, $M+1^+$), 448 (M-tBu$^+$ 88), 312 (M-tBu-$MeOC_6H_4CHO^+$ 50), 253 (50); [found: C, 64.50; H, 7.76; N 2.68%; $C_{26}H_{35}NO_6S$ requires C, 64.41; H, 7.40; N, 2.78%;].

Adduct with 2-methoxybenzaldehyde (**69d**).- The product was isolated and characterised as a yellow foam (90%) which consisted of a 2:1 mixture of diastereoisomers.

υ_{max} (nujol mull)/cm^{-1} 3400 (OH), 3200, 1730, 1660 and 1040; δ_H 1.11 (9H, s, OC*Me*3), 1.15 (9H, s, C*Me*3), 1.55 (3H, d, *J* 6.8, C*H*3), 3.85 (2H, s, OC*H3* major isomer), 3.95 (1H, s, OC*H3* minor isomer), 4.16 (0.66H, d, *J* 9.0, SOC*H* major isomer), 4.35 (0.33H, d, *J* 9.0, SOC*H* minor isomer), 5.10-5.25 (1H, 2 x quintet, *J* 6.8, C*H*Me), 5.31 (0.66H, d, *J* 10.5, C*H*OH, major isomer), 5.45 (0.33H, d, *J* 10.5, C*H*OH minor isomer), 5.90 (1H, bd, *J* 6.8, NH, both diastereoisomers), 6.85-7.00 (2H, m, aromatic *H*), 7.20-7.35 (1H, m, aromatic *H*), 7.40-7.58 (4H, m, aromatic *H*), 8.00-8.10 (1H, m, aromatic *H*); δ_C (major diastereosiomer) 20.66 (q), 26.95 (q), 27.08 (q), 38.05 (s), 44.21 (d), 54.94 (q), 69.22 (d), 69.83 (d), 82.45 (s), 110.0 (d), 120.3 (d), 125.2 (d), 125.6 (d), 127.2 (d), 127.9 (d), 128.9 (d), 131.6 (d), 139.4 (s), 139 (s), 140.4 (s), 141.9 (s), 155.6 (s), 165.0 (s), 177.4 (s); *m/z* (FAB) 504 (24, $M+1^+$), 448 (M-tBu$^+$ 31), 312 (M-tBu-$MeOC_6H_4CHO^+$ 10), 253 (30) [found: m/z 504.2393, C, 63.3; H, 7.46; N 2.73%; $C_{26}H_{35}NO_6S$-0.16 H_2O requires m/z 504.2419, C, 64.2; H, 7.46; N, 2.73%;].

Adduct with 4-nitrobenzaldehyde (**69e**) The product was isolated as a brown foam (70%). $[\alpha]_D^{25}$= -91° (c=0.35, chloroform); υ_{max} (nujol mull)/cm^{-1} 3580-3020, 1720, 1660, 1480, 1340 and 1040; δ_H 1.17 (9H, s, CMe3), 1.32 (9H, s, CMe3), 1.52 (d, *J* 6.78, C*H*3), 4.45 (1H, d, *J* 5.13, SOC*H*), 5.18 (1H, bd, *J* 5.13, C*H*OH),

5.42 (1H, quintet, *J* 6.8, C*H*Me), 5.88 (1H, bd, *J* 6.8, NH), 7.26-7.94 (6H, m, aromatic *H*), 8.22 (2H, d, *J* 9.0, aromatic *H*); δ_C 21.96 (q), 27.76 (q), 28.02 (q), 38.78 (s), 45.12 (d), 71.26 (d), 72.04 (d), 83.10 (s), 123.9 (d), 126.5 (d), 127.5 (d), 127.9 (d), 128.5 (d), 132.6 (d), 139.0 (s), 141.0 (s), 143.0 (s), 147.9 (s), 165.0 (s), 177.0 (s); *m/z* (FAB) 519 (6, $M+1^+$), 463 (M-tBu^+,75), 253 (50) [MH^+ found 519.2145, $C_{26}H_{35}N_2O_7S$ requires 519.2165].

Adduct with 2-nitrobenzaldehyde (**69f**).- The product was isolated as a brown foam (80%).

$[\alpha]_D^{25}$= -147° (c=1.15, chloroform); υ_{max} (nujol mull)/cm^{-1} 3580-3020, 1720, 1660, 1480, 1340 and 1040; δ_H 1.10 (9H, s, CMe_3), 1.15 (9H, s, CMe_3), 1.52 (d, *J* 6.78, CH_3), 4.45 (1H, d, *J* 4.50, SOC*H*), 5.29 (1H, quintet, *J* 6.78, C*H*Me), 5.82 (1H, d, *J* 4.5, C*H*OH), 5.96 (1H, bd, *J* 6.78, NH), 7.42-8.07 (8H, m, aromatic *H*); δ_C 20.95 (q), 27.31 (q), 27.50 (q). 38.31 (s), 44.37 (d), 69.15 (d), 69.74 (d), 83.39 (s), 124.9 (d), 125.7 (d), 125.8 (d), 128.4 (d), 129.0 (d), 129.4 (d), 132.1 (d), 133.7 (d), 135.6 (d), 139.0 (s), 142.2 (s), 147.0 (s), 164.8 (s), 177.4 (s); *m/z* (FAB) 519 (16, $M+1^+$), 463 (M-tBu^+, 100) [found MH^+ 519.2143, $C_{26}H_{35}N_2O_7S$ requires 519.2165].

Adduct with trimethylacetaldehyde (**69g**).- The product was isolated as a colourless oil (90%).

$[\alpha]_D^{25}$= -125° (c=0.48, chloroform); υ_{max} (nujol mull)/cm^{-1} 3410-3380, 1700, 1640 and 1060; δ_H 0.91 (9H, s, CMe_3), 1.15 (9H, s, CMe_3), 1.27 (9H, s, CMe_3), 1.54 (d, *J* 6.8, CH_3), 3.69 (1H, dd, *J* 6.0, 1.5, C*H*OH), 3.83 (1H, d, *J* 1.5, OH), 4.36 (1H, d, *J*, 6.2, C*H*SO), 5.25 (1H, quintet, *J* 6.8, C*H*Me), 5.90 (1H, bd, *J* 6.8, NH), 7.42-7.56 (3H, m, aromatic *H*), 7.97 (1H, dd, *J* 6.0, 3.0, aromatic *H*); δ_C 20.98 (q), 26.01 (q), 27.73 (q), 27.63 (q), 36.46 (q), 38.30 (s), 44.57 (d) 66.62 (d), 78.78 (d), 83.0 (s), 125.9 (d), 128.4 (d), 131.9 (d) 139.0 (s), 142.0 (s), 166 (s),

177.0 (s); *m/z* (FAB) 454 (24, M+1$^+$), 398 (M-tBu$^+$, 100), 253 (50) [found M$^+$ 454.2630, $C_{24}H_{38}NO_5S$ requires 454.2627].

Adduct with 2-methylpropanal (**69h**).- The product was isolated as a white solid as a 7:1 mixture of two diastereoisomers (75%). Recrystallisation furnished the pure major diastereoisomer.

$[\alpha]_D^{25}$= -111° (c=0.55, chloroform); υ_{max} (nujol mull)/cm^{-1} 3410-3380, 1700, 1640 and 1060; δ_H 0.94 (3H, d, *J* 6.6, CHC*H*$_3$), 1.01 (3H, d, *J* 6.6, CHC*H*$_3$), 1.16 (9H, s, CMe3), 1.29 (9H, s, CMe3), 1.54 (d, *J* 6.6, NCHC*H*$_3$), 3.70 (2H, m, O*H* and C*H*OH), 3.83 (1H, d, *J*, 4.4, C*H*SO), 5.25 (1H, quintet, *J* 6.6, C*H*Me), 5.89 (1H, bd, *J* 6.6, NH), 7.42-7.56 (3H, m, aromatic *H*), 7.96-8.02 (1H, m, aromatic *H*); δ_C 17.74 (q), 19.10 (q), 21.11 (q), 27.37 (q), 27.76 (q), 32.56 (d), 38.00 (s), 44.57 (d), 69.57 (d), 75.48 (d), 83.16 (s), 125.9 (d), 128.4 (d), 131.8 (d), 139.8 (s), 142.0 (s), 166.0 (s), 177.3 (s); *m/z* (FAB) 440 (31, M+1$^+$), 384 (M-tBu$^+$ 100), 312 (M-tBu-2-methylpropanal, 8) [found: C, 62.50; H, 8.66; N 3.08%; $C_{23}H_{37}NO_5S$ requires C, 62.80; H, 8.48; N, 3.19%].

Adduct with acetaldehyde (**69i**). The product (a 3:1 mixture of diastereoisomers) was isolated as a white solid (60%).

υ_{max} (nujol mull)/cm^{-1} 3410-3380, 1700, 1640 and 1090; δ_H 0.94 (2.25H, d, *J* 6.6, CH(OH)C*H*$_3$), 1.01 (0.75H, d, *J* 6.6, CH(OH)C*H*$_3$), 1.16 (9H, s, CMe3), 1.29 (9H, s, CMe3), 1.50 (2.25H, d, *J* 6.6 CHC*H*$_3$), 1.51 (0.75H, d, *J* 6.6, CHC*H*$_3$), 3.68-3.84 (2H, m, C*H*OH and OH, both isomers), 4.50 (0.75H, m, C*H*SO), 4.70 (0.25H, m, C*H*SO), 5.25 (0.75H, quintet, *J* 6.6, CH), 5.47 (0.25H, quintet, *J* 6.6, CH), 5.89-5.95 (1H, 2 x bd, *J* 6.6, NH), 7.42-7.56 (3H, m, aromatic *H*), 7.96-8.02 (1H, m, aromatic *H*); δ_C 20.92 (q), 20.98 (q), 27.34 (q), 27.80 (q), 32.60 (d), 38.50 (s), 44.86 (d), 68.15 (d), 75.41 (d), 83.00 (s), 125.8 (d), 126.3 (d), 128.3 (d), 131.7 (d), 139.8 (s), 141.3 (s), 165.2 (s), 177.5 (s); *m/z* (FAB) 412 (44, M+1$^+$), 356 (M-tBu$^+$ 100) [found M+1$^+$ 412.2189, $C_{21}H_{32}NO_5S$ requires 412.2158].

4.4.3 Synthesis of racemic β-hydroxyesters (±)-(**71**)

(±)-(**71**)

To a stirred solution of diisopropylamine (19.7mmol) in tetrahydrofuran (10cm^3) at 0°C was added a solution of n-butyllithium (19.7mmol) in hexane. Following stirring for 0.2 hrs the solution was cooled to -78°C and a solution of t-butyl acetate (19.68mmol) in tetrahydrofuran (2cm^3) was added dropwise. After stirring for 0.5 hrs a solution of the aldehyde (19.7mmol) in tetrahydrofuran (10cm^3) was added dropwise. The reaction was quenched with aqueous hydrochloric acid (10cm^3) after 0.2h. The organic phase was removed, the aqueous phase extracted with dichloromethane (3 x 50cm^3) and the combined organic extracts washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The product hydroxy esters were isolated by f.c. (10% ethyl acetate/petroleum ether).

t-Butyl 3-hydroxy-3-phenylpropanoate (±)-(**71a**). The product was isolated as a colourless oil (73%).

υ_{max} (neat)/cm^{-1} 3410 and 1700; δ_H ($CDCl_3$, 270 MHz) 1.20 (9H, s, C-Me3), 2.55 (2H, CH_2), 3.49 (1H, d, OH), 4.96 (1H, quintet, *J* 8.25, C*H*OH), 7.10 (5H, m, aromatic H); δ_C ($CDCl_3$) 27.89 (q), 44.21 (t), 70.22 (d), 81.20 (s), 125.6 (d), 127.5 (d), 128.2 (d), 142.7 (s), 171.6 (s); *m/z* (C.I.); 223 (M^++1, 20), 167 (M^+-tBu, 60), 149 (M^+-tBu-H_2O, 100) (Found: C, 70.0; H, 8.19. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.16%).

tert-Butyl 3-hydroxy-3-(2-methoxyphenyl)propanoate (±)-(**71b**). The product was isolated as a white solid (60%).

υ_{max} /cm^{-1} 3450, 2850 and 1695; δ_H ($CDCl_3$, 270 MHz) 1.38 (9H, s, CMe_3) 2.75-2.49 (2H, qd, *J* 16, 9, 4.5, CH_2), 3.51 (1H, d, *J* 5.13, OH), 3.80 (3H, s, OMe), 5.25 (1H, quintet, *J* 4.50, C*H*OH), 6.80 (1H, d, *J* 8.25, aromatic H), 6.90 (1H, dt, *J* 7.51, 1.0, aromatic H), 7.20 (1H, dt, *J* 7.51, 2.0, aromatic H), 7.35 (1H, dd, *J* 7.51, 2.0, aromatic H); δ_C ($CDCl_3$) 28.02 (q), 42.59 (t), 55.17 (q), 66.46 (d), 81.05 (s), 110.1 (d), 120.6 (d), 126.6(d), 128.4 (d), 130.6 (s), 155.9 (s), 172.0 (s); *m/z* (E.I.); 252 (M^++1, 2), 196 (M^+-tBu, 15), 137 (M^+-methoxy-benzaldehyde+1, 100) (Found: C, 66.4; H, 8.01. $C_{14}H_{20}O_3$ requires C, 66.6; H, 7.99%).

tert-Butyl 3-hydroxy-4-methylpentanoate (±)-(**71c**). The product was isolated as a colourless oil (75%).

υ_{max} /cm^{-1} 3500 and 1730; δ_H ($CDCl_3$, 270 MHz) 0.92 (3H, d, *J* 6.78, CH*Me*), 0.94 (3H, d, *J* 6.78, CH*Me*), 1.47 (9H, s, C*Me*$_3$), 1.70 (1H, bhextet, *J* 7.5, C*H*Me_2), 2.64-2.45 (2H, qd, *J* 15.9, 9.07, 3.39, CH_2), 3.33 (1H, d, *J* 3.97, OH), 3.73 (1H, bsextet, *J* 6.00, C*H*OH); δ_C ($CDCl_3$) 17.41 (q) 18.10 (q), 27.80 (q), 39.34 (t), 72.43 (d), 80.60 (s), 172.5 (s); *m/z* (C.I.); 189 (M^++1, 2), 133 (M^+-tBu, 70), 115 (M^+-tBu-H_2O, 100) (Found: C, 63.5; H, 10.9. $C_{10}H_{20}O_3$ requires C, 63.8; H, 10.7%).

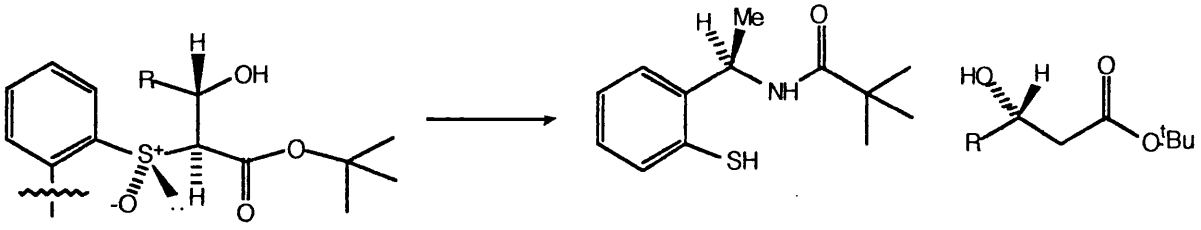
tert-Butyl 3-hydroxy-3-(2-nitrophenyl)propanoate (±)-(**71d**). The product was isolated as a yellow solid (49%).

υ_{max} /cm^{-1} 3475, 1695 and 1340; δ_H ($CDCl_3$, 270 MHz) 1.46 (9H, s, CMe_3), 2.92-2.53 (2H, qd, *J* 16.67, 9.16, 2.74, CH_2), 3.91 (1H, bs, OH), 5.61 (1H, dd, *J* 9.16,2.74, C*H*OH), 7.43 (1H, dt, *J* 7.50, 1.50, aromatic H), 7.67 (1H, dt, *J* 7.50, 1.50, aromatic H), 7.89 (1H, dd, *J* 7.50, 1.50, aromatic H), 7.93 (1H, dd, *J* 7.50, 1.50, aromatic H); δ_C ($CDCl_3$) 27.99 (q), 43.14 (t), 66.55 (d), 81.83 (s), 124.4 (d), 128.2 (d), 128.3 (d), 133.6 (d), 138.1 (s), 147.3 (s), 171.7 (s); m/z 212 (80), 197

(70), 164 (60), 146 (100) [Found: C, 58.5; H, 6.49; N, 5.26. $C_{13}H_{17}NO_5$ requires C, 58.4; H, 6.49; N, 5.24%].

tert-Butyl 3-hydroxy-3-(2-aminophenyl)propanoate (±)-(**71e**). To a stirred solution of (±)-(**71d**) (0.10g, 0.38mmol) in 10% aqueous tetrahydrofuran (22cm^3) was added portionwise aluminium amalgam (generated by dipping commerical baking foil in 2% aqueous mercuric chloride, washing in ethanol and diethyl ether) (1.35g, 56mmol). The resulting suspension was stirred at ambient temperature for 16h and then diluted with dichloromethane (50cm^3) and filtered through glass wool. The resulting residue was washed with dichloromethane (50cm^3) and the combined organics dried over anhydrous sodium sulphate. The filtrate was evaporated at reduced pressure and the product was isolated by column chromatography as a yellow solid (0.068g, 77%). υ_{max} /cm^{-1} 3475, 400, 1700; δ_H ($CDCl_3$, 270 MHz) 1.48 (9H, s, C-Me_3), 2.60-3.12 (2H, qd, *J* 16.67, 9.16, 2.74, CH_2), 3.86 (3H, bs, OH/NH_2), 5.12 (1H, dd, *J* 9.16,2.74, C*H*OH), 6.65 (1H, dt, *J* 7.50, 1.50, aromatic H), 6.80 (1H, dt, *J* 7.50, 1.50, aromatic H), 7.02 (1H, dd, *J* 7.50, 1.50, aromatic H), 7.10 (1H, dd, *J* 7.50, 1.50, aromatic H); δ_C ($CDCl_3$) 28.09 (q), 28.09 (q), 40.10 (t), 70.35 (d), 81.57 (s), 116.8 (d), 118.2 (d), 125.6 (s), 127.2 (d), 128.8 (d), 145.3 (s), 172.7 (s); m/z 237 (M^+ 10), 181 (15), 146 (15), 122 (35) [found (EI) M^+ 237.1370, $C_{21}H_{32}NO_5S$ requires 237.1365].

4.4.5 Reductive cleavage of the aldol adducts.



(**69a-i**) (R)-(+)-(**70**) (R)-(+)-(**71**)

To a stirred solution of the aldol adduct (0.2mmol) in 10% aqueous tetrahydrofuran ($16.5cm^3$) was added portionwise aluminium amalgam (generated by dipping commerical baking foil in 2% aqueous mercuric chloride, washing in ethanol and diethyl ether) (32.2mmol). The resulting suspension was stirred at ambient temperature for 16h and then diluted with dichloromethane ($50cm^3$) and filtered through glass wool. The resulting residue was washed with dichloromethane ($50cm^3$) and the combined organics dried over anhydrous sodium sulphate. The filtrate was evaporated at reduced pressure and the title compounds recovered by column chromatography. The yields are given in table 3. In all cases β-hydroxy esters (**71**) and thiol (R)-(+)-(**70**) were identified by comparision of their proton NMR spectrum with that of the authentic materials described above.

Reduction of adduct (**69a**). (R)-(+)-(**71**) was isolated as a colourless oil (85%); $[\alpha]_D^{25} = +32^o$ (c=0.20, Chloroform3); $[\alpha]_D^{25} = +13$ (c=0.15, EtOH). (R)-(+)-(**70**) was isolated as a white solid (80%).

Reduction of adduct (**69f**). (R)-(+)-(**71e**) was isolated as a yellow solid (65%); $[\alpha]_D^{25} = +9.7^o$ (c=0.53, Chloroform3).

Reduction of adduct (**69d**) Compound (**71b**) was isolated as a white solid (68%).

Reduction of adduct (**69h**)- Compound (**71c**) was isolated as a colourless oil (75%) with (R)-(+)-(**70**) isolated as a white solid (73%).

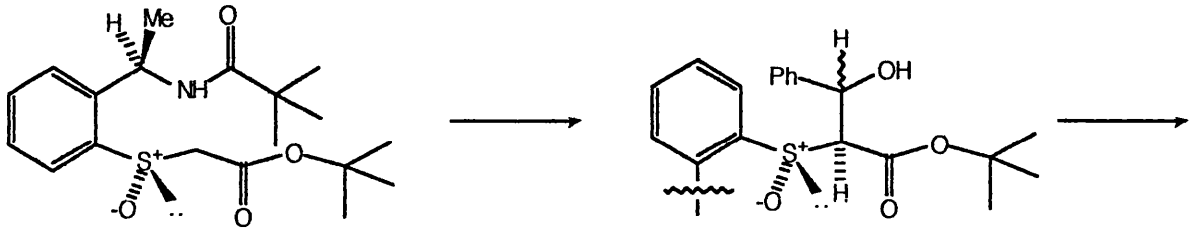
Proof of enantiomeric purity of β-hydroxy esters with shift reagent X-tert-Butyl-3-hydroxy-3-phenylpropanoate (**71a**).- Addition of 0.15 equivalents of shift reagent to racemic material shifted the O-*t*Bu resonances to δ1.77 and 1.71. Addition of the same quantity of (**71a**) to the enantiomerically enriched material gave only a single peak at δ1.70 (270 MHz NMR).

tert-Butyl 3-hydroxy-3-(2-aminophenyl)propanoate (**71e**) .- Addition of 0.15 equivalents of shift reagent to racemic material shifted the O-*t*Bu resonances to δ1.66 and 1.63. Addition of the same quantity of (**71e**) to the enantiomerically enriched material gave only a single peak at δ1.66 (270 MHz NMR).

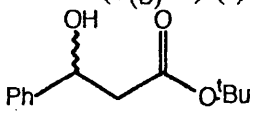
tert-Butyl 3-hydroxy-3-(2-methoxyphenyl)propanoate (**71b**).- Addition of 0.28 equivalents of shift reagent to racemic material shifted the O-*t*Bu resonances to δ1.84 and 1.77. The OMe peaks also shifted to δ3.98 and 3.87. Addition of the same quantity of (**71b**) to the enantiomerically enriched material resulted in the same peak splitting in a 1:3 ratio (270 MHz NMR).

tert-Butyl 3-hydroxy-4-methylpentanoate (**71c**)- Addition of 0.15 equivalents of shift reagent to racemic material shifted the O-*t*Bu resonances to δ1.85 and 1.77. Addition of the same quantity of (**71c**) to the enantiomerically enriched material resulted in the same peak splitting in a 7:1 ratio (270 MHz NMR).

4.4.6 Mechanistic studies.



($S_{(S)}$ R)-(-)-(**67**)

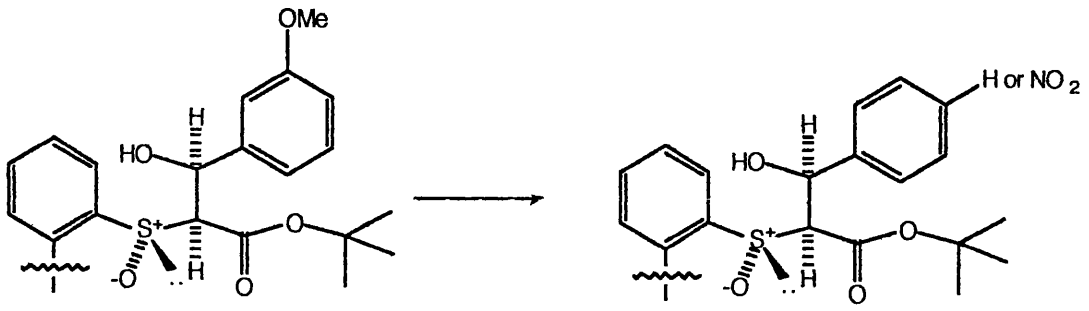


(**71**)

tert-Butyl bromide (2.0 cm^3, 17.4 mmol) was added dropwise to a cooled (O°C) stirred suspension of magnesium (0.375g, 15.6 mmol) in diethyl ether (6 cm^3). The mixture was stirred until all the magnesium had been consumed at which point the resultant grey-brown solution was added dropwise at to a stirred solution of ($S_{(S)}$ R)-(-)-(**67**) (0.280g, 0.78 mmol) in THF (40 cm^3) at -78°C. The white suspension was stirred for 1.5 hrs at -78°C before a solution of benzaldehyde (0.71cm^3, 7.0 mmol) in THF (10 cm^3) was added dropwise to the solution, which was stirred at -78°C for 0.5 hrs. Saturated ammonium chloride solution (50 cm^3) was added at low temperature and the organic phase removed. The aqueous phase was extracted with ethyl acetate (3 x 25 cm^3) and the organic phases were combined, washed with brine and dried over sodium sulphate. Removal of solvent and flash chromatography furnished (**69a**) (0.392g, 92%) which by ^{1}H-NMR consisted of a 1:1 mixture of two diastereoisomers. The peaks from one of the isomers matched those previously described for (**69a**). The other diastereoisomer was responsible for the following peaks.

δ_H 0.82 (9H, s, OCMe3), 1.20 (9H, s, CMe3), 1.56 (d, *J* 6.8, C*H*3), 4.18 (1H, d, *J* 10, SOC*H*), 5.38 (1H, bd, *J* 10, PhC*H*), 5.24 (1H, quintet, *J* 6.8, C*H*Me), 5.94 (1H, bd, *J* 6.8, NH), 7.24-8.00 (9H, m, aromatic *H*). A sample of this mixture was cleaved using Al/Hg amalgam to give a β-hydroxy ester (**71a**) (80%) which was shown by a chiral shift NMR experiment to be racemic.

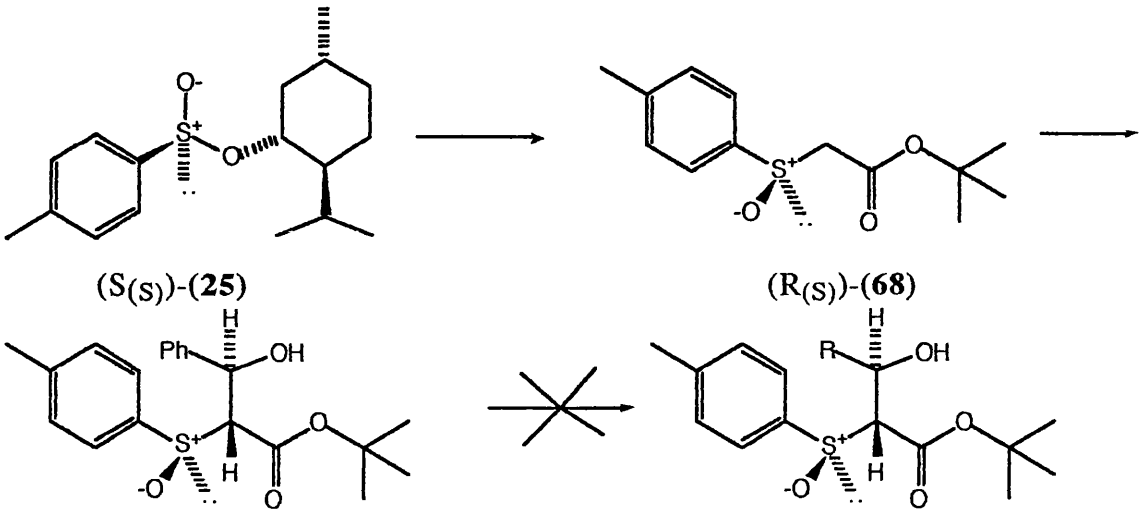
4.4.7 Crossover experiment to prove reversibility of aldol reaction.



(69c) **(69a)** or **(69e)**

tert-Butyl bromide (0.080 cm^3, 0.65 mmol) was added dropwise to a cooled (O^oC) stirred suspension of magnesium (0.017g, 0.65 mmol) in diethyl ether (1 cm^3). The mixture was stirred until all the magnesium had been consumed at which point the resultant grey-brown solution was added dropwise at -78°Cto a stirred solution of **(69c)** (0.100g, 0.20mmol) in THF (10cm^3). After stirring at -78°C for 1.5 hr benzaldehyde (0.050 cm^3, 0.50mmol) (or 4-nitrobenzaldehyde (0.076g, 0.50mmol)) was added and stirring continued for 16 hr at room temperature. At the end of this time the reaction was quenched by the addition of aqueous saturated ammonim chloride (10cm^3) and extracted with ethyl acetate (3 x 10 cm^3). The combined organics were dried (sodium sulphate) and the solvent removed. Purification by f.c. was used to remove the excess aldehyde and for the isolation of the reaction products which were identified by comparison of their ^{1}H-NMR spectra with those described above as **(69a)** (56mg, 58%, a single diastereoisomer) and ($S_{(S)}$ R)-(-)-**(67)** (30mg, 20%).

4.4.8 Literature aldol reaction and attempted crossover.



Bromoethane (0.93 cm^3, 12.47mmol) was added dropwise to a stirred suspension of magnesium (0.392g, 13.71mmol) in diethyl ether (17cm^3) and the mixture stirred at ambient temperature until all the magnesium had been consumed. Di-isopropylamine (1.59cm^3, 11.33mmol) was added dropwise and the reaction mixture was heated at reflux for 1 hr. The resultant red suspension was cooled to -40°C and tetrahydrofuran (1cm^3) was added. A solution of *tert*-butyl acetate (1.07cm^3, 7.93mmol) and ($S_{(S)}$)-(**25**) (1.00g, 3.40mmol) in tetrahydrofuran (1cm^3) and diethyl ether (8cm^3) was added dropwise over 1h. The reaction was stirred for 6h at -40°C then allowed to warm to ambient temperature and stirred at this temperature for 16h. Saturated ammonium chloride solution (10cm^3) was added and the organic phase separated. The aqueous phase was extracted with ethyl acetate (3 x 10cm^3) and the combined organic extracts were washed with brine (25 cm^3), dried over sodium sulphate. Removal of the solvent followed by flash chromatography (50/50 ethyl acetate/petroleum ether) gave (R)-(**68**) (0.607g, 70%) as a colourless oil.

δ_H ($CDCl_3$); 1.40 (9H, s, CMe_3), 2.42 (3H, s, *Me*), 3.55-3.60 (1H, d, *J* 13.6, CH_{AB}), 3.77-3.82 (1H, d, *J* 13.6, CH_{AB}), 7.32 (2H, d, *J* 7.9, aromatic), 7.56 (2H, d, *J* 7.9, aromatics). Identical to known literature sample.

tert-Butyl bromide (1.00cm^3, 7.84mmol) was added dropwise to a cooled (O°C) stirred suspension of magnesium (0.188g, 7.84 mmol) in diethyl ether (3cm^3). The mixture was stirred until all the magnesium had been consumed at which point the

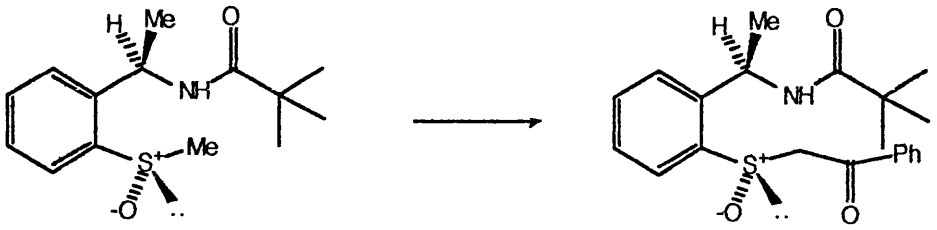
resultant grey-brown solution was added dropwise to a stirred solution of (R)-(**68**) (0.100g, 0.38 mmol) in THF (20 cm^3) at -78°C. The white suspension was stirred for 1.5 hrs at -78°C before a solution of benzaldehyde (0.36cm^3, 1.14 mmol) in THF (5 cm^3) was added dropwise to the solution, which was stirred at -78°C for 8 h. Saturated ammonium chloride solution (25 cm^3) was added and the organic phase removed. The aqueous phase was extracted with ethyl acetate (3 x 25 cm^3) and the organic phases were combined, washed with brine and dried over sodium sulphate. Removal of solvent and flash chromatography furnished the aldol product (0.130g, 95%).

δ_H ($CDCl_3$); 1.23 (9H, s, C*Me*$_3$), 2.43 (3H, s, *Me*), 3.64 (1H, d, *J* 6.0, C*H*SO), 5.10 (1H, d, *J* 6.0, C*H*OH), 7.32 (7H, m, aromatic), 7.56 (2H, d, *J* 8.1, aromatics). Identical to known literature sample.

tert-Butyl bromide (0.080 cm^3, 0.65 mmol) was added dropwise to a cooled (O°C) stirred suspension of magnesium (0.017g, 0.65 mmol) in diethyl ether (1 cm^3). The mixture was stirred until all the magnesium had been consumed at which point the resultant grey-brown solution was added dropwise at -78°Cto a stirred solution of the aldol product (0.072g, 0.20 mmol) in THF (10 cm^3). After stirring at -78°C for 1.5h benzaldehyde (0.050 cm^3, 0.50 mmol) (or 4-nitrobenzaldehyde (0.076g, 0.50mmol)) was added and stirring continued for 16 hr at room temperature. At the end of this time the reaction was quenched by the addition of aqueous saturated ammonim chloride (10 cm^3) and extracted with ethyl acetate (3 x 10 cm^3). The combined organics were dried (sodium sulphate) and the solvent removed. Examination of the ^1H NMR spectra of the crude reaction mixture (after removal of excess aldehyde) showed only peaks corresponding to the starting adduct.

4.5 Synthesis Of β-Ketosulphoxides

4.5.1 Literature synthesis



($S_{(S)}$ R)-(-)-(**82**) ($S_{(S)}$ R)-(-)-(**85**)

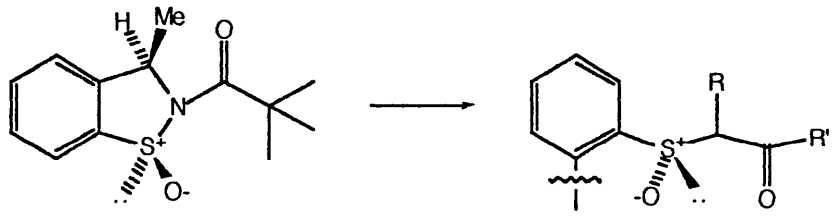
To a stirred solution of diisopropylamine (0.23cm^3, 1.63mmol) in tetrahydrofuran (0.60cm^3) at 0°C was added dropwise a solution of *tert*-butyllithium in pentane (0.87cm^3, 1.48mmol). The resulting solution was stirred at 0°C for 0.5h, then cooled to -60°C and a solution of ($S_{(S)}$ R)-(-)-(**82**) (0.10g, 0.37mmol) in tetrahydrofuran (0.95cm^3) added dropwise. The reaction mixture was allowed to warm upto 0°C over a period of 0.5h and stirred for 1.0h at this temperature. To the reaction mixture was added a 10% solution (v/v) of ethyl benzoate in tetrahydrofuran (0.50cm^3, 0.37mmol) and the reaction stirred at 0°C for 1.0h,then quenched with saturated aqueous ammonium chloride (2cm^3). The organic phase was removed and the aqueous phase extracted with dichloromethane (3 x 5cm^3), the combined organic extracts washed with brine, dried over sodium sulphate and the filtrate evaporated at reduced pressure. The ($S_{(S)}$ R)-(-)-(**85**) was isolated after column chromatography (50% ethyl acetate/petroleum ether) (0.13g, 94%).

Melting point 133-4°C (petroleum ether/dichloromethane).$[\alpha]_D^{25}$ -142.5° (c=0.59, Chloroform3); υ_{max} (nujol mull)/cm^{-1} 3321, 1681, 1645 and 1056; ∂_H ($CDCl_3$, 270 MHz) 1.20(9H, s, C*Me*$_3$), 1.55 (3H, d, *J* 6.75, CH*Me*), 4.55 (1H, d, *J* 13.5, CH_{AB}), 4.95 (1H, d, *J* 13.5, CH_{AB}), 5.54 (1H, quintet, *J* 6.75, C*H*Me), 6.05 (1H, bd, *J* 6.75, NH), 7.62-7.35 (5H, m, aromatics), 7.80 (1H, d, *J* 4.5, aromatics), 8.00(2H, d, *J* 4.5Hz, aromatics); ∂_C ($CDCl_3$) 22.20 (q,), 27.42 (q), 38.45 (s), 45.85 (d), 63.62 (t), 125.6 (d), 126.7 (d), 128.2 (d), 128.7 (d, 2C), 129.0 (d, 2C), 131.9 (d), 134.0 (s), 136.2 (s), 140.7 (s), 143.3 (s), 177.8 (s), 191.9 (s). Mass spectra.(F.A.B) 372

(MH^+,100), 319 (6), 305 (7). [found: C, 67.7; H, 6.75; N 3.84%; $C_{13}H_{19}NO_3S$ requires C, 67.9; H, 6.74; N, 3.77%].

Additonal peaks in the ^1H NMR corresponding to the minor diastereoisomer at at; 1.19 (9H, C*Me*$_3$), 1.50 (3H, CH*Me*), 4.36-4.43 (1H, C*H*$_2$), 4.99 (1H, C*H*Me), 5.35-5.43 (1H, C*H*$_2$).

4.5.2 Direct synthesis of the β-ketosulphoxides



($S_{(S)}$ R)-(+)-*cis*-(**59**)

To a stirred solution of sodium bis(trimethylsilylamide) (1.00cm^3, 1.00mmol, 1.00M in tetrahydrofuran) at -78°C was added dropwise a solution of the ketone (1.00mmol) in toluene (1cm^3) and the resultant solution stirred at this temperature for 1h. A solution of ($S_{(S)}$ R)-(+)-*cis*-(**59**) (0.100g, 0.40mmol) in toluene (1cm^3) was then added dropwise to the solution and stirring continued at -78°C for 1h, then the reaction allowed to warm to ambient temperature. The solution stirred at ambient temperature until examination by t.l.c. all ($S_{(S)}$ R)-(+)-*cis*-(**59**) consumed. The reaction was quenched with saturated aqueous ammonium chloride (5cm^3) and then diluted with water (5cm^3). The organic phase was removed and the aqueous phase extracted with ethyl acetate (3x5cm^3). The combined organics were washed with brine (15cm^3) and then dried over sodium sulphate. The filtrate was evaporated at reduced pressure and the residue was columned on silica (50-100% ethyl acetate petroleum ether) to give the required adducts.

4.5.3 Data for synthesised acyclic β-ketosulphoxides

The adduct with acetophenone was isolated as a colourless solid (78%). R'=phenyl, R=H ($S_{(S)}$ R)-(-)-(**85**)- see previous synthesis for spectroscopic details.

The adduct with 4-methoxyacetophenone was isolated as a colourless solid (quantitative). R'=4-methoxyphenyl, R=H, ($S_{(S)}$ R)-(-)-(**86**).

M.p. 75°C (ethyl acetate petroleum ether) $[\alpha]_D^{25}$= -198.7° (c=0.15, Chloroform3); υ_{max} (nujol mull)/cm^{-1} 3459, 1710, 1663, 1032; δ_H ($CDCl_3$) 1.18 (9H, s, C*Me3*), 1.54 (3H, d, *J* 7.0, CHC*H3*), 3.87 (3H, s, O*Me*), 4.46 (1H, d, *J* 14.3, C*H*), 4.86 (1H, d, *J* 14.3, C*H*), 5.51 (1H, quintet, *J* 7.0, C*H*Me), 6.01 (1H, bd, *J* 7.0, N*H*), 6.89-6.92 (2H, d, *J* 7.0, aromatics), 7.34-7.47 (3H, m, aromatics), 7.75-7.78 (1H, m, aromatics), 7.95-7.97 (2H, d, *J* 7.0, aromatic); δ_C ($CDCl_3$) 22.06 (q), 27.34 (q), 38.37 (s), 45.37 (d), 55.43 (q), 63.44 (t), 113.8 (2C, d), 125.4 (d), 126.7 (d), 128.1 (d), 129.3 (s), 131.5 (2C, d), 131.8 (d), 140.7 (s), 143.2 (s), 164.2 (s), 177.7 (s), 190.0 (s); m/z (F.A.B.) 402 (MH^+, 81), 384 (2), 251 (5), 150 (100); [found: C, 64.1; H, 6.88; N, 3.39; $C_{22}H_{27}NO_4S$-0.5 H_2O requires C, 64.4; H, 6.83; N, 6.41;]

Additonal peaks in the ^1H NMR for the diastereoisomeric mixture at; 1.47 (3H, CH*Me*), 3.86 (3H, O*Me*), 4.37 (1H, CH_2), 5.33 (1H, CH_2), 4.95 (1H, C*H*Me), 6.28 (1H, NH).

The adduct with 2'-methylacetophenone was isolated as a colourless solid (73%). R'=2'methylphenyl, R=H, ($S_{(S)}$ R)-(-)-(**87**).

M.p. 78°C (ethyl acetate petroleum ether); $[\alpha]_D^{25}$= -151.4° (c=0.62, Chloroform3); υ_{max} (nujol mull)/cm^{-1} 3459, 1730, 1665, 1034; δ_H ($CDCl_3$) 1.17 (9H, s, C*Me3*), 1.54 (3H, d, *J* 6.7, CHC*H3*), 2.46 (3H, s, *Me*), 4.49 (1H, d, *J* 15.0, C*H*), 4.85 (1H, d, *J* 15.0, C*H*), 5.46 (1H, quintet, *J* 6.7, C*H*Me), 6.02 (1H, bd, *J* 6.7, N*H*), 7.25 (2H, m, aromatics), 7.40 (4H, m, aromatics), 7.81 (2H, bt, *J* 6.7, aromatics); δ_C ($CDCl_3$) 21.57 (q), 22.05 (q), 27.37 (q), 38.41 (s), 46.06 (d), 65.88 (t), 125.6 (d), 125.9 (d), 126.7 (d), 128.3 (d), 130.5 (d), 131.8 (d), 132.1 (d), 132.5 (d), 135.7 (s), 139.8 (s), 140.9 (s), 143.0 (s), 177.6 (s), 194.3 (s); m/z (F.A.B.) 386 (MH^+, 100), 368 (5), 285 (10), 253 (10); [found: C, 67.0; H, 7.29; N, 3.26; $C_{22}H_{27}NO_3S$-0.5 H_2O requires C, 67.0; H, 7.15; N, 3.55;]

The adduct with pinacolone was isolated as a colourless solid (70%). R'=*tert*-butyl, R=H, ($S_{(S)}$ R)-(-)-(**88**)

M.p. 124°C (ethyl acetate petroleum ether); $[\alpha]_D^{25}$=- 160.8° (c=0.365, Chloroform3); υ_{max} (nujol mull)/cm^{-1} 3460, 1705, 1660, 1034; δ_H ($CDCl_3$) 1.11 (9H, s, C*Me3*), 1.17 (9H, s, C*Me3*), 1.53 (3H, d, *J* 7.0, CHC*H3*), 4.07 (1H, d, *J* 15.6, C*H*), 4.55 (1H, d, *J* 15.6, C*H*), 5.50 (1H, quintet, *J* 7.0, C*H*Me), 6.01 (1H, bd, *J* 7.0, N*H*), 7.40-7.49 (3H, m, aromatics), 7.83 (1H, d, *J* 7.7, aromatics); δ_C ($CDCl_3$) 22.35 (q), 25.43 (q), 27.31 (q), 38.31 (s), 44.53 (s), 45.93 (d), 62.96 (t), 125.6 (d), 126.9 (d), 128.1 (d), 131.8 (d), 141.0 (s), 143.7 (s), 177.6 (s), 207.6 (s); m/z (F.A.B.) 352 (MH^+, 100) 334 (8), 251 (10); [found: C, 65.1; H, 8.35; N, 3.88; $C_{19}H_{29}NO_3S$ requires C, 65.0 ;H, 8.26; N, 3.99;]

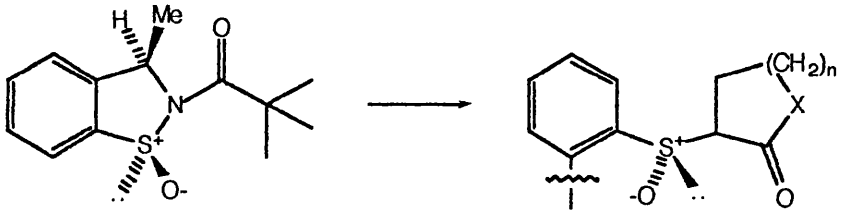
Additonal peaks in the ^1H NMR for the diastereoisomeric mixture at; 1.15 (9H, C*Me3*), 1.20 (9H, C*Me3*), 1.28 (3H, CH*Me*), 3.92 (1H, CH_2), 4.80 (1H, CH_2), 5.13 (1H, C*H*Me).

The adduct with propiophenone was isolated as a white foam (75%) as a 51:49 mixture of diastereoisomers. R'=phenyl, R=methyl, ($S_{(S)}$ R)-(-)-(**89**)

υ_{max} (nujol mull)/cm^{-1} 3460, 1705, 1660, 1034; δ_H ($CDCl_3$) Major; 1.19 (9H, s, C*Me3*), 1.50 (3H, d, *J* 7.1, CHC*H3*), 1.76 (3H, d, *J* 7.0, CHC*H3*), 5.42 (1H, q, *J* 7.1, C*H*CH3), 5.71 (1H, quintet, *J* 7.0, C*H*CH3), 5.98 (1H, bd, *J* 7.0, N*H*), 7.12-7.68 (7H, m, aromatic), 8.02 (2H, d, *J* 7.5, aromatic); Minor; 1.21 (9H, s, C*Me3*), 1.34 (3H, d, *J* 7.1, CHC*H3*), 1.44 (3H, d, *J* 7.0, CHC*H3*), 5.58 (1H, q, *J* 7.1, C*H*CH3), 5.84 (1H, quintet, *J* 7.0, C*H*CH3), 5.92 (1H, bd, *J* 7.0, N*H*), 7.12-7.68 (7H, m, aromatic), 7.78 (2H, d, *J* 7.5, aromatic); δ_C ($CDCl_3$) 13.07 (q, 0.5C), 13.14 (q, 0.5C), 21.97 (d, 0.5C), 22.23 (d, 0.5C), 27.33 (q, 3C), 38.28 (s, 1C), 44.67 (d, 0.5C), 45.14 (d, 0.5C), 63.07 (t, 0.5C), 66.12 (t, 0.5C), 126.2 (d, 0.5), 126.4 (d, 1C), 127.2 (d, 0.5C), 127.3 (d, 0.5C), 127.5 (d, 0.5C), 128.3 (d, 1C), 128.4 (d, 2C), 128.5 (d, 1C), 128.8 (d, 1C), 131.6 (d, 0.5C), 132.0 (d, 0.5C), 133.4 (d, 1C), 135.5 (s, 0.5C), 136.4 (s, 0.5C), 138.2 (s, 0.5C), 139.7 (s, 0.5C), 144.0 (s, 0.5C),

144.7 (s, 0.5C), 177.3 (s, 0.5C), 177.6 (s, 0.5C), 196.4 (s, 0.5C), 196.7 (s, 0.5C). m/z (F. A. B) 386 (MH^+, 100), 275 (12), 252 (13). [found m/z 386.1772 $C_{22}H_{27}NO_3S$ MH^+ requires 386.1790]

4.5.4 Synthesis of cyclic β-ketosulphoxides



($S_{(S)}$ R)-(+)-*cis*-(**82**)

The adduct with butyrolactone was isolated as a mixture of diastereoisomers (76%) and was recrystallised for characterisation purposes. X=O, n=1, ($S_{(S)}$ R)-(-)-(**90**)

M.p. 108-9°C (ethyl acetate petroleum ether); $[\alpha]_D^{25}$= -165.6° (c=0.16, Chloroform3); υ_{max} (nujol mull)/cm^{-1} 3305, 1760, 1638, 1068, 1015; δ_H ($CDCl_3$) 1.19 (9H, s, C*Me3*), 1.56 (3H, d, *J* 7.0, CHC*H3*), 2.30 (1H, m, C*H*), 3.00 (1H, m, C*H*), 4.05 (1H, dd, *J* 9.5, 7.5, C*H*), 4.35 (1H, m, C*H*), 4.50 (1H, td, *J* 9.0, 5.3, C*H*), 5.25 (1H, quintet, *J* 7.0, C*H*Me), 5.96 (1H, bd, *J* 7.0, N*H*), 7.42-7.59 (3H, m, aromatics), 7.89 (1H, d, *J* 7.5, aromatics); δ_C ($CDCl_3$) 19.00 (t), 21.41 (q), 27.05 (q), 38.14 (s), 44.92 (d), 61.50 (d), 67.17 (t), 124.4 (d), 126.5 (d), 127.9 (d), 131.9 (d), 139.0 (s), 142.0 (s), 171.7 (s), 177.7 (s); m/z (F.A.B.) 338 (MH^+, 100), 254 (19), 237 (10); [found: m/z 338.1457 $C_{17}H_{23}NO_4S$ requires (MH^+) 338.1426]

The adduct with cyclopentanone was isolated as a mixture of diastereoisomers (45%) and purified by further column chromatography to furnish a single diastereoisomer as a white foam. X=CH_2, n=1, ($S_{(S)}$ R)-(-)-(**91**).

υ_{max} (nujol mull)/cm^{-1} 3460, 1705, 1660, 1034; δ_H ($CDCl_3$) 1.14 (9H, s, C*Me3*), 1.49 (3H, d, *J* 6.8, CHC*H3*), 1.60-1.90 (2H, m, C*H*), 2.00-2.45 (3H, m, C*H*), 2.45-2.60 (1H, m, C*H*), 3.45 (1H, t, *J* 8.6, C*H*), 5.05 (1H, quintet, *J* 6.8, C*H*Me), 6.01 (1H, bd, *J* 6.8, N*H*), 7.38-7.50 (3H, m, aromatics), 7.83 (1H, m, aromatics);

δ_C ($CDCl_3$) 20.08 (t), 20.37 (t), 21.41 (q), 27.28 (q), 38.47 (s), 38.89 (t), 45.93 (d), 69.35 (d), 125.3 (d), 126.7 (d), 128.1 (d), 131.5 (d), 140.2 (s), 141.1 (s), 177.7 (s), 211.6 (s); m/z (F.A.B.) 336 (MH^+, 100); [found: m/z 336.1633 $C_{18}H_{25}NO_3S$ requires (MH^+) 336.1619.]

The adduct with cyclohexanone was isolated as a colourless solid (78%) which was recrystallised from dichloromethane for analytical purposes. X=CH_2, n=2, ($S_{(S)}$ R)-(-)-(**92**).

M.p. 133°C (dichloromethane); $[\alpha]_D^{25}$= -153.9° (c=0.395, Chloroform3); υ_{max} (nujol mull)/cm^{-1} 3240, 1707, 1642, 1023; δ_H ($CDCl_3$) 1.17 (9H, s, C*Me3*), 1.51 (3H, d, *J* 6.8, CHC*H3*), 1.62-2.62 (8H, m, C*H2*), 4.08 (1H, t, *J* 7.5, C*H*), 5.40 (1H, quintet, *J* 6.8, C*H*Me), 5.90 (1H, bd, *J* 6.8, N*H*), 7.40-7.50 (3H, m, aromatics), 7.90 (1H, m, aromatics); δ_C ($CDCl_3$) 21.37 (q), 23.26 (t), 26.43 (t), 26.66 (t), 27.47 (q), 38.01 (s), 42.36 (t), 45.51 (d), 72.62 (d), 126.4 (d), 126.7 (d), 128.3 (d), 131.7 (d), 141.3 (2, s), 177.5 (s), 205.7 (s); m/z (F.A.B.) 350 (MH^+, 100), 332 (5), 253 (15); [found: m/z 350.1782; $C_{19}H_{27}NO_3S$ requires (MH^+) 350.1790]

The adduct with cycloheptanone was isolated as a mixture of diastereoisomers (98%). X=CH_2, n=3, ($S_{(S)}$ R)-(-)-(**93**).

υ_{max} (nujol mull)/cm^{-1} 3460, 1705, 1660, 1034; δ_H ($CDCl_3$) Major 1.16 (9H, s, C*Me3*), 1.54 (3H, d, *J* 6.8, CHC*H3*), 1.60-2.50 (10H, m, C*H2*), 4.20 (1H, dd, *J* 11.3, 4.5, C*H*), 5.40 (1H, quintet, *J* 6.8, C*H*Me), 5.97 (1H, bd, *J* 6.8, N*H*), 7.38-7.52 (3H, m, aromatics), 7.83 (1H, d, *J* 7.7, aromatics); Minor 1.16 (9H, s, C*Me3*), 1.56 (3H, d, *J* 6.8, CHC*H3*), 1.60-2.50 (10H, m, C*H2*), 3.80 (1H, dd, *J* 12.0, 6.0, C*H*), 5.20 (1H, quintet, *J* 6.8, C*H*Me), 5.82 (1H, bd, *J* 6.8, NH), 7.38-7.52 (3H, m, aromatics), 7.78 (1H, d, *J* 7.7, aromatics); δ_C ($CDCl_3$) major 21.34 (q), 23.77 (t), 25.46 (t), 27.15 (q), 27.57 (t), 29.58 (t), 38.18 (s), 44.14 (t), 45.08 (d), 74.92 (d), 125.0 (d), 126.1 (d), 127.7 (d), 131.5 (d), 141.5 (s), 142.9 (s), 177.2 (s), 209.4 (s);

minor 20.95 (q), 23.61 (t), 24.94 (t), 27.15 (q), 27.63 (t), 28.83 (t), 38.18 (s), 43.43 (t), 44.24 (d), 72.56 (d), 125.9 (d), 126.3 (d), 127.9 (d), 131.5 (d), 139.0 (s), 140.3 (s), 177.2 (s), 207.3 (s); m/z (F.A.B.) 364 (MH^+, 100); [found: m/z 364.1943; $C_{20}H_{29}NO_3S$ requires (MH^+) 364.1946]

The adduct with cyclodecanone was isolated as a mixture of diastereomisomers (88%). X=CH_2, n=6, ($S_{(S)}$ R)-(-)-(**94**).

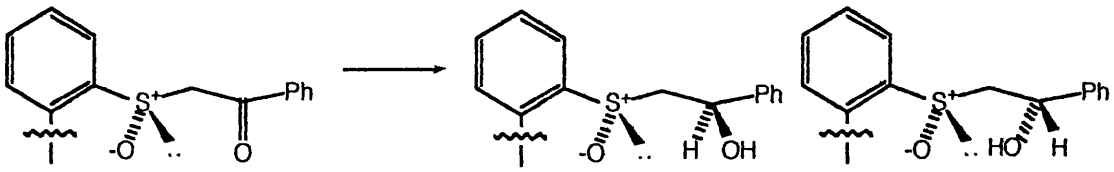
υ_{max} (nujol mull)/cm^{-1} 3460, 1705, 1660, 1034; δ_H ($CDCl_3$) Major 1.16 (9H, s, C*Me*$_3$), 1.50 (3H, d, *J* 6.7, CHC*H*$_3$), 1.10-1.90 (14H, m, C*H*$_2$), 2.20-2.60 (2H, m, C*H*$_2$), 4.45 (1H, m, C*H*), 5.35 (1H, quintet, *J* 6.7, C*H*Me), 5.80 (1H, bd, *J* 6.7, N*H*), 7.40-7.55 (3H, m, aromatics), 7.83 (1H, m, aromatics); Minor 1.17 (9H, s, C*Me*$_3$), 1.57 (3H, d, *J* 6.7, CHC*H*$_3$), 1.10-1.90 (14H, m, C*H*$_2$), 2.20-2.60 (2H, m, C*H*$_2$), 4.66 (1H, m, C*H*), 5.47 (1H, quintet, *J* 6.7, C*H*Me), 6.00 (1H, bd, *J* 6.7, NH), 7.40-7.55 (3H, m, aromatics), 7.83 (1H, m, aromatics); δ_C ($CDCl_3$) Major 22.07 (q), 22.83-26.27 (11t), 26.82 (q), 37.85 (s), 44.17 (d), 44.37 (t), 76.06 (d), 125.4 (d), 125.9 (d), 127.4 (d), 131.5 (d), 139.0 (s), 143.9 (s), 176.9 (s), 209.0 (s); Minor 21.05 (q), 22.83-26.27 (11t), 26.82 (q), 37.75 (s), 42.85 (t) 43.98 (d), 71.91 (d), 125.9 (d), 127.6 (d), 127.6 (d), 131.8 (d), 138.8 (s), 142.3 (s), 176.7 (s), 207.0 (s); m/z (F.A.B.) 406 (MH^+, 100), 253 (15); [found: m/z 406.2412; $C_{23}H_{35}NO_3S$ requires (MH^+) 406.2416]

The adduct with cyclopentadecanone was isolated as a mixture of diastereomisomers X=CH_2, n=10, ($S_{(S)}$ R)-(-)-(**95**).

υ_{max} (nujol mull)/cm^{-1} 3463, 1710, 1668, 1037; δ_H ($CDCl_3$); 1.16 (9H, s, C*Me*$_3$), 1.50 (3H, d, *J* 7.1, CH*Me*), 1.60-1.80 (22H, m, C*H*$_2$), 2.00-2.50 (4H, m, C*H*$_2$), 4.06 (0.5H, dd, *J* 12.2, 2.9, C*H*), 4.53 (0.5H, m, C*H*), 5.30 (0.5H, quintet, *J* 7.1, C*H*Me), 5.53 (0.5H, quintet, *J* 7.1, C*H*Me), 5.83 (0.5H, bd, *J* 7.1, N*H*), 5.91 (0.5H, bd, *J* 7.1, N*H*), 7.31-7.52 (3H, m, aromatics), 7.66-7.76 (1H, m, aromatics); δ_C major; 21.47 (q), 25.66 (t), 25.79 (t), 26.01 (t), 26.14 (t, 2C), 26.24 (t), 26.37 (t),

26.76 (t), 26.82 (t), 26.99 (t), 27.12 (t), 27.28 (q, 3C), 27.57 (t), 38.30 (s), 43.95 (t), 44.50 (d), 72.67 (d), 125.5 (d), 126.3 (d), 128.0 (d), 131.9 (d), 139.1 (s), 142.6 (s), 177.3 (s), 207.5 (s). minor; 21.76 (q), 25.66 (t), 25.79 (t), 26.01 (t), 26.14 (t, 2C), 26.24 (t), 26.37 (t), 26.76 (t), 26.82 (t), 26.99 (t), 27.12 (t), 27.28 (q, 3C), 27.57 (t), 38.21 (s), 43.62 (t), 44.63 (d), 75.48 (d), 126.1 (d), 126.5 (d), 127.8 (d), 132.0 (s), 139.7 (s), 144.3 (s), 177.2 (s), 207.5 (s). m/z (F.A.B.) 476 ($M+H^+$, 100). [found: m/z 476.3171; $C_{28}H_{45}NO_3S$ requires (MH^+) 476.3198]

4.6 Reduction Of The Acyclic β-Ketosulphoxides



($S_{(S)}$ R)-(-)-(**85**) ($S_{(S)}$ R, S)-(-)-(**96**) ($S_{(S)}$ R, S)-(-)-(**97**)

4.6.1 General reduction protocols

Diisobutylaluminium hydride. To a stirred solution of the β-ketosulphoxide (0.093g, 0.25mmol) in tetrahydrofuran 1.2cm^3) was added dropwise at -78°C a solution of diisobutylaluminium hydride (0.50cm^3, 0.50mmol) in hexanes. The resulting reaction mixture was stirred at this temperature for 1.0h and then quenched with saturated aqueous ammonium chloride (2cm^3). The resulting mixture was treated with a few drops of aqueous hydrochloric acid (2M). The organic phase was then removed, the aqueous phase extracted with dichloromethane (3 x 5cm^3) and the combined organic extracts washed with brine, dried over sodium sulphate and the filtrate evaporated at reduced pressure. The title compound was isolated after column chromatography (50% ethyl acetate/petroleum ether) for evaluation by ^{1}H NMR spectroscopy..

Sodium borohydride reduction. To a stirred suspension of sodium borohydride (0.010g, 0.27mmol) in tetrahydrofuran (3cm^3) at -78°C was added dropwise a solution of the ketone (0.099g, 0.27mmol) in tetrahydrofuran (3cm^3). The resultant reaction mixture was stirred at -78°C for 2h and then saturated aqueous ammonium chloride (6cm^3) added. The organic phase was removed and the resultant aqueous phase extracted with ethyl acetate (3x10cm^3). The combined organic phases were dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure to yield the crude compound (0.102g, 100%) for evaluation by ^{1}H NMR spectroscopy.

Tetrabutylammonium borohydride reduction. To a suspension of tetrabutylammonium borohydride (0.068g, 0.26mmol) in tetrahydrofuran (3cm^3) at 0°C was added a solution of the ketone (0.102g, 0.27mmol) in tetrahydrofuran (3cm^3). The reaction mixture was stirred at ambient temperature for 48h. Hydrogen peroxide solution (3%)

($10cm^3$) and aqueous sodium hydroxide (2M, $5cm^3$) were added and the mixture stirred for 0.25h. The mixture was extracted with dichloromethane ($3x15cm^3$) and the combined organic phases dried over anhydrous sodium sulphate. The filtrate was evaporated at reduced pressure to yield the crude compound (0.131g, 130%) for evaluation by ^1H NMR spectroscopy.

Sodium borohydride/cerium (III) chloride reduction. To a stirred suspension of cerium (III) chloride-heptahydrate (0.201g, 0.52mmol) and the ketone (0.097g, 0.26mmol) in methanol ($3cm^3$) at 0°C was added in one portion sodium borohydride (0.066g, 1.69mmol). The resultant reaction mixture was stirred at ambient temperature for 2.5h and then saturated aqueous ammonium chloride ($6cm^3$) added. The organic phase was removed and the resultant aqueous extracted with ethyl acetate ($3x10cm^3$). The combined organic phases dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure to yield the crude compound (0.102g, 100%) for evaluation by ^1H NMR spectroscopy.

Sodium triacetoxyborohydride reduction. To a stirred suspension of sodium triacetoxyborohydride (0.229g, 1.08mmol) in tetrahydrofuran ($3cm^3$) at 0°C was added a solution of the ketone (0.106g, 0.29mmol) in tetrahydrofuran ($3cm^3$). The reaction mixture was stirred at ambient temperature for 48h. Water ($10cm^3$) added and extracted with ethyl acetate ($3x10cm^3$). The combined organic phases dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure to yield the crude compound (0.124g, 115%) for evaluation by ^1H NMR spectroscopy

Lithium aluminium hydride reduction. To a stirred suspension of lithium aluminium hydride (0.012g, 0.32mmol) in tetrahydrofuran ($3cm^3$) at -78°C was added dropwise a solution of the ketone (0.099g, 0.27mmol) in tetrahydrofuran ($3cm^3$). The resultant reaction mixture was stirred at -78°C for 2.5h and then saturated aqueous ammonium chloride ($6cm^3$) added. The organic phase was removed and the resultant aqueous extracted with ethyl acetate ($3x10cm^3$). The combined organic phases dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure to yield the crude compound (0.098g, 97%) for evaluation by ^1H NMR spectroscopy.

*Diisobutylaluminium hydride/zinc bromide reductions.*To a stirred solution of the ketone (0.40mmol) in tetrahydofuran ($1cm^3$) at ambient temperature was added a solution of zinc bromide ($1.00cm^3$, 1.00mmol, 1.00M in tetrahydrofuran). The mixture was then stirred at this temperature for 1h then cooled to -78°C. A solution of diisobutylaluminium hyride ($1.00cm^3$, 1.00mmol, 1.00M in tetrahydrofuran) was added and the resultant mixture was stirred at -78°C for 1h. Quenched sequentially with methanol ($1cm^3$) and saturated aqueous sodium tartrate ($1cm^3$) and allowed to warm to ambient temperature. Sufficient aqueous hydrochloric acid (2M) was added to dissolve the white precipitate. The resultant aqueous phase was then extracted with ethyl acetate ($3x10cm^3$) and the combined organics washed with brine ($15cm^3$) and dried over sodium sulphate. The filtrate was evaporated at reduced pressure and the residue columned on silica (50-100% ethyl acetate petroleum ether) to give the titled compounds.

4.6.2 Data for the diisobutylaluminium hydide reduction

Reduction of acetophenone adduct ($S_{(S)}$ R)-(-)-(**85**) - formation of ($S_{(S)}$ R, S)-(-)-(**96**) (73%)

M.p. 94-6°C (dichloromethane hexane). $[\alpha]_D^{25}$ -151.5° (c=0.13, Chloroform$_3$). ν_{max} (nujoll mull/cm^{-1}) 3451, 3354, 1661, 1496, 1029. ∂_H ($CDCl_3$, 270 MHz) 1.19 (9H, s, C*Me*$_3$), 1.53 (3H, d, *J* 7.0, CH*Me*), 2.98-3.05 (1H, dd, *J* 13.5, 1.5, CH_{AB}), 3.26-3.36 (1H, dd, *J* 13.5, 12.0, CH_{AB}), 5.28-5.33 (2H, m, C*H*Me and C*H*OH), 5.93 (1H, bd, *J* 7.0, NH), 7.26-7.57 (8H, m, aromatics), 8.04-8.07 (1H, m, aromatics); ∂_C 22.18 (q), 27.34 (q, 3C), 38.53 (s), 45.31 (d), 64.35 (t), 68.53 (d), 124.9 (d), 125.6 (d, 2C), 126.6 (d), 127.8 (d), 128.5 (d, 2C), 128.7 (d), 131.4 (d), 140.6 (s), 141.4 (s), 142.2 (s), 177.9 (s). Mass spectra.(C.I) 374 ($M+1^+$, 100), 340 (40), 238 (50), 204 (80). [Found; C, 66.0; H, 7.44; N, 3.55. $C_{21}H_{27}NO_3S$-0.5H_2O requires C, 66.0; H, 7.32; N, 3.66%.]

Data for the β-hydroxysulphide (R, S)-(**98**) (10%).

∂_H ($CDCl_3$, 270 MHz) 1.20 (9H, s, C*Me*$_3$), 1.45 (3H, d, *J* 7.0, CH*Me*), 2.20 (1H, exchangeable, OH), 2.95-3.00 (1H, dd, *J* 13.5, 10.5, CH_{AB}), 3.29-3.35 (1H, dd, *J* 13.5, 3.0, CH_{AB}), 4.40-4.45 (1H, dd, *J* 10.5, 3.0, C*H*OH), 5.85 (1H, quintet, *J* 7.0, C*H*Me), 6.11 (1H, d, *J* 7.0, N*H*), 7.21-7.55 (8H, m, aromatics), 7.92-7.98 (1H, m, aromatics). m/z (F.A.B.) 356 ($M-H^+$, 15), 340 (40), 204 (50).

Reduction of 4-methoxyacetophenone adduct ($S_{(S)}$ R)-(-)-(**86**) - formation of ($S_{(S)}$ R, S)-(-)-(**99**) (90%).

M.p 90°C (dichloromethane hexane). $[\alpha]_D^{25}$ -177.4° (c=0.42, Chloroform$_3$). υ_{max} (nujoll mull/cm^{-1}) 3332, 1641, 1513, 1026. δ_H ($CDCl_3$, 400MHz) 1.02 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.8, CH*Me*), 2.81-2.85 (1H, dd, *J* 13.7, 2.0, CH_{AB}), 3.03-3.09 (1H, dd, *J* 13.7, 10.7, CH_{AB}), 3.60 (3H, s, O*Me*), 4.50 (1H, bs, O*H*), 5.09-5.18 (2H, m, C*H*OH and C*H*Me), 6.00 (1H, bd, *J* 6.8, N*H*), 6.67 (2H, d, *J* 8.8, aromatics), 7.12 (2H, d, *J* 8.8, aromatics), 7.26-7.34 (3H, m, aromatics), 7.84-7.85 (1H, m, aromatics). δ_C 21.50 (q), 27.31 (q, 3C), 38.49 (s), 45.42 (d), 55.18 (s), 64.53 (s), 68.09 (s), 113.9 (d, 2C), 124.1 (d), 126.6 (d), 126.9 (d, 2C), 127.1 (d), 131.4 (d), 134.5 (s), 140.8 (s), 141.5 (s), 159.1 (s), 177.8 (s). m/z (F.A.B) 404 (MH^+, 35), 386 (75), 253 (30). [found: C, ; H, ; N, $C_{22}H_{29}NO_4S$ required C, ; H, ; N, ;]-submitted

Reduction of 2-methylacetophenone adduct ($S_{(S)}$ R)-(-)-(**87**) - formation of ($S_{(S)}$ R, S)-(-)-(**101**).

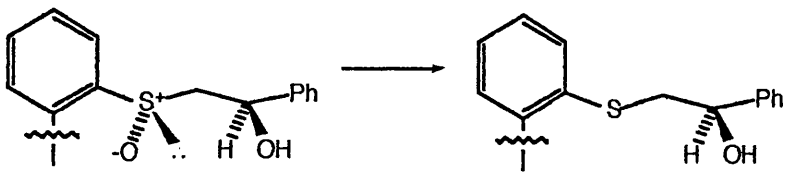
M.p. 96-8°C (dichloromethane hexane). $[\alpha]_D^{25}$ -133.0 (c=0.115, Chloroform). υ_{max} (nujoll mull/cm^{-1}) 3334, 1638, 1522, 1020. δ_H ($CDCl_3$) 1.19 (9H, s, C*Me*$_3$), 1.52 (3H, d, *J* 7.0, CH*Me*), 2.05 (3H, s, *Me*), 2.82-2.86 (1H, dd, *J* 13.7, 1.5, CH_{AB}), 3.22-3.28 (1H, dd, *J* 13.7, 10.1, CH_{AB}), 4.22 (1H, d, *J* 3.4, O*H*), 5.25 (1H, quintet, *J* 7.0, C*H*Me), 5.50 (1H, bd, *J* 11.3, C*H*OH), 5.91 (1H, bd, *J* 7.0, N*H*), 7.05 (1H, d, *J* 7.3, aromatics), 7.14 (H, td, *J* 7.4, 1.6, aromatics), 7.23 (1H, t, *J* 7.3,

aromatics), 7.44-7.59 (4H, m, aromatics), 8.10 (1H, m, aromatics). δ_C 18.41 (q), 21.26 (q), 27.40 (q, 3C), 38.60 (s), 45.01 (d), 61.75 (s), 65.41 (s), 125.0 (d), 125.5 (d), 126.5 (d), 126.7 (d,), 127.6 (d), 128.6 (d), 130.4 (d), 131.5 (d), 133.6 (s), 140.0 (s), 140.2 (s), 141.4 (s), 177.8 (s). m/z (F.A.B) 388 (MH^+, 100), 370 (30), 253 (30). [found: C, 66.0; H, 7.72; N, 3.26. $C_{22}H_{29}NO_3S$-0.75H_2O requires C, 65.9; H, 7.62; N, 3.50]

Reduction of pinacolone adduct ($S_{(S)}$ R)-(-)-(**88**) - formation of (R, S)-(-)-(**103**) (55%).

M.p. 134-6°C (dichloromethane hexane). $[\alpha]_D^{25}$= -57.8° (c=0.735, chloroform) υ_{max} (nujoll mull/cm^{-1}) 3346, 1635. δ_H ($CDCl_3$) 0.86 (9H, s, C*Me3*), 1.19 (9H, s, C*Me3*), 1.38 (3H, d, *J* 6.8, CH*Me*), 2.63-2.72 (1H, dd, *J* 13.4, 10.8, CH_{AB}), 2.96-3.01 (1H, dd, *J* 10.8, 1.7, CH_{AB}), 3.23-3.28 (1H, dd, *J* 13.4, 1.7, C*H*OH), 5.75 (1H, quintet, *J* 6.8, C*H*Me), 6.05 (1H, bd, *J* 6.8, N*H*), 7.15-7.30 (3H, m, aromatics), 7.40-7.50 (1H, m, aromatics). δ_C 22.67 (q), 25.69 (q, 3C), 27.34 (q, 3C), 37.74 (s), 38.50 (s), 39.05 (t), 46.61 (d), 74.73 (d), 124.6 (d), 127.3 (d), 127.5 (d), 128.6 (d), 132.8 (s), 146.7 (s), 177.4 (s). m/z (F.A.B.) 338 ($M+H^+$, 40), 320 (5), 280 (18), 204 (45). [found C, 67.6; H, 9.38, N, 3.54. $C_{19}H_{31}NO_2S$ requires C, 67.7; H, 9.20; N, 4.15]

4.6.3 Reduction of the β-hydroxysulphoxide to the β-hydroxysulphide



($S_{(S)}$ R, S)-(-)-(**96**) (R, S)-(**98**)

To a stirred yellow slurry of triphenylphosphine (0.247g, 0.94mmol) and iodine (0.244g, 0.96mmol) in acetonitrile (6cm^3) was added in a single portion sulphoxide ($S_{(S)}$ R, S)-(-)-(**96**) (0.300g, 0,80mmol) and stirring continued for 5m. To this

suspension was added solid sodium iodide (0.234g, 1.56mmol) and the resultant black mixture stirred at ambient temperature for 2h and then diluted with ethyl acetate ($15cm^3$). The organic phase was washed sequentially with saturated aqueous sodium thiosulphate ($15cm^3$) and water ($10cm^3$), dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure. The required compound was purified using flash column chromatography on silica (0-50% ethyl acetate petroleum ether as eluant) and isolated as a white foam. Spectral details identical to those observed in DIBAL-H reduction.

4.6.4 Data for the diisobutylaluminium hydide zinc (II) bromide reduction

Reduction of acetophenone adduct ($S_{(S)}$ R)-(-)-(**85**) - formation of ($S_{(S)}$ R, R)-(-)-(**96**) (80%)

M.p. 54°C (dichloromethane hexane). $[\alpha]_D^{25}$= - 94.5° (c=0.22, chloroform); υ_{max} (nujoll mull/cm^{-1}) 3453, 3355, 1662, 1029. δ_H ($CDCl_3$) 1.19 (9H, s, C*Me3*), 1.49 (3H, d, *J* 7.0, CHC*H3*), 3.05-3.11 (1H, dd, *J* 2.0, 13.2, C*H*), 3.36-3.45 (1H, dd, *J* 13.2, 10.1, C*H*), 4.57 (1H, bs, OH), 5.30 (1H, quintet, *J* 7.0, C*H*Me), 5.46 (1H, dd, *J* 10.5, 1.5, C*H*), 5.91 (1H, bd, *J* 7.0, NH), 7.26-7.53 (8H, m, aromatics), 8.00 (1H, m, aromatics); δ_C ($CDCl_3$) 21.70 (q), 27.44 (q), 38.53 (s), 44.99 (d), 62.24 (t), 71.49 (d), 124.9 (d), 125.8 (2C, d), 126.2 (d), 128.1 (d), 128.6 (2C,s, d), 129.0 (d), 131.8 (d), 141.1 (s), 141.9 (s), 142.0(s), 177.6 (s); m/z (F.A.B.) 374 (MH^+, 100), 150 (65); [found: C, 64.7; H, 7.21; N, 3.33; $C_{21}H_{27}NO_3S$-H_2O requires C, 64.5; H, 7.42; N, 3.53.]

Reduction of 2'-methylacetophenone adduct ($S_{(S)}$ R)-(-)-(**87**) -formation of ($S_{(S)}$ R, R)-(-)-(**102**) (90%).

M.p. 52°C (dichloromethane hexane). $[\alpha]_D^{25}$= -72.1° (c=0.52, chloroform); υ_{max} (nujol mull)/cm^{-1} 3333, 1639, 1021; δ_H ($CDCl_3$) 1.19 (9H, s, C*Me3*), 1.47 (3H, d, *J* 6.8, CHC*H3*), 2.36 (3H, s, *Me*), 3.00-3.40 (2H, 2xdd, *J* 1.8, 9.9, 13.4, CH_{AB}), 4.51 (1H, bs, OH), 5.31 (1H, quintet, *J* 6.8, C*H*Me), 5.31 (1H, bd, *J* 9.9, C*H*), 5.89 (1H, bd, *J* 6.8, NH), 7.15 (3H, m, aromatics), 7.42 (1H, m, aromatics), 7.55 (3H, m, aromatics), 8.00 (1H, m, aromatics); δ_C ($CDCl_3$) 18.83 (q), 21.49 (q), 27.32 (q), 38.40 (s), 44.55 (d), 61.69 (t), 67.53 (d), 124.6 (d), 125.6 (d), 126.0 (d), 126.4 (d), 127.6 (2C,s, d), 128.8 (d), 130.4 (d), 131.7 (d), 134.0 (s), 140.0 (s), 141.2 (s), 141.9(s), 177.5 (s); m/z (F.A.B.) 388 (MH^+, 95), 370 (60), 353 (5); [found: C, 65.1; H, 7.51; N, 3.28; $C_{22}H_{29}NO_3S$-H_2O requires C, 65.2; H, 7.65; N, 3.45]

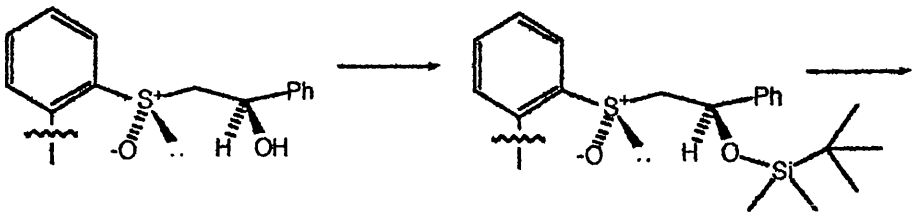
Reduction of 4-methoxyacetophenone adduct ($S_{(S)}$ R)-(-)-(**86**) - formation of ($S_{(S)}$ R, R)-(-)-(**100**) (quantitative).

M. p. 50°C (dichloromethane hexane). $[\alpha]_D^{25}$ -81.7° (c=0.235, Chloroform3); υ_{max} (nujol mull)/cm^{-1} 3334, 1640, 1513, 1026. δ_H ($CDCl_3$) 1.18 (9H, s, C*Me3*), 1.46 (3H, d, *J* 7.0, CHC*H3*), 2.99-3.05 (1H, dd, *J* 2.4, 13.0, C*H*), 3.32-3.41 (1H, dd, *J* 13.0, 9.7, C*H*), 4.65 (1H, bs, OH), 5.25-5.40 (2H, m, C*H*Me, C*H*OH), 6.04 (1H, bd, *J* 7.0, NH), 6.86 (2H, d, *J* 8.6, aromatics), 7.32 (2H, d, *J* 8.6, aromatics), 7.40-45 (1H, m, aromatics), 7.45-7.55 (2H, m, aromatics), 8.00 (1H, m, aromatics); δ_C ($CDCl_3$) 21.62 (q), 27.37 (q), 38.45 (s), 44.94 (d), 55.20 (q), 62.63 (t), 70.84 (d), 113.9 (2C, d), 124.8 (d), 126.2 (d), 127.1 (2C, d), 128.8 (d), 131.7 (s), 134.3 (d), 141.3 (s), 141.9 (s), 159.3(s), 177.5 (s); m/z (F.A.B.) 404 (MH^+, 47), 386 (100), 253 (60). [found: C, 63.0; H, 7.18; N, 3.29; $C_{22}H_{29}NO_4S$-H_2O requires C, 62.7; H, 7.36; N, 3.29]

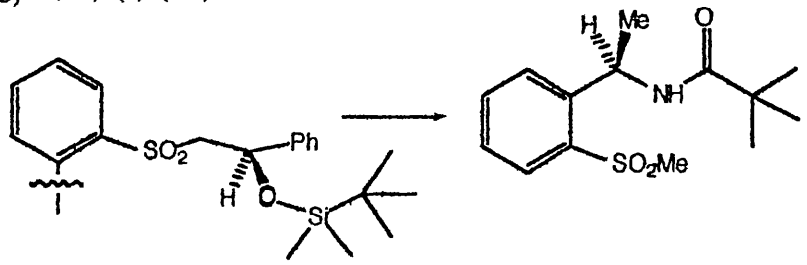
Reduction of pinacolone adduct ($S_{(S)}$ R)-(-)-(**88**) formation of ($S_{(S)}$ R, R)-(-)-(**105**) (90%).

M. p.65-6°C (dichloromethane hexane). $[\alpha]_D^{25}$= -112° (c=0.25, chloroform); υ_{max} (nujol mull)/cm^{-1} ; δ_H ($CDCl_3$) 0.91 (9H, s, C*Me3*), 1.17 (9H, s, C*Me3*), 1.50 (3H, d, *J* 6.8, CHC*H3*), 2.91-3.06 (2H, qd, , *J* 23.2, 9.8, 1.5, C*H*$_{ABX}$), 3.95 (1H, dd, *J* 9.8, 1.5, C*H*OH), 4.05 (1H, bs, OH), 5.29 (1H, quintet, *J* 6.8, C*H*Me), 5.95 (1H, bd, *J* 6.8, N*H*), 7.40-7.55 (3H, m, aromatics), 8.00 (1H, d, *J* 7.70, aromatics); δ_C ($CDCl_3$) 21.64 (q), 25.41 (q), 27.35 (q), 35.27 (s), 38.43 (s), 44.83 (d), 56.99 (t), 76.25 (d), 124.9 (d), 126.0 (d), 128.8 (d), 131.6 (d), 141.2 (s), 142.1 (s), 177.4 (s); m/z (F.A.B.) 354 (MH^+, 100), 340 (18). [found: C, 63.0; H, 8.92; N, 3.66; $C_{19}H_{31}NO_3S$-$0.5H_2O$ requires C, 63.0; H, 8.84;N, 3.87;]

4.6.5 Attempted formation of styrene oxide- formation of methyl sulphone (R)-(**109**)



($S_{(S)}$ R, S)-(-)-(**96**)



(R, S)-(**106**) (R)-(**109**)

To a stirred solution of the alcohol ($S_{(S)}$ R, S)-(-)-(**96**) (0.379g, 1.02mmol) and imidazole (0.297g, 4.60mmol) in DMF (5cm^3) was added in a single portion *tert*-butyldimethylsilyl chloride (0.337g, 2.30mmol). The mixture was stirred at ambient temperature for 16h and then poured into a saturated aqueous solution of ammonium chloride (25cm^3). Extracted with ethyl acetate (3 x 15cm^3) and the combined organics dried over anhydrous sodium sulphate. The filtrate was evaporated at reduced pressure to give the crude product (0.444g, 89%) which was used directly.

δ_H ($CDCl_3$); -0.05 (3H, s, Si*Me*), 0.01 (3H, s, Si*Me*), 0.16 (9H, s, SiC*Me*$_3$), 1.20 (9H, s, C*Me*$_3$), 1.56 (3H, d, *J* 7.0, CH*Me*), 2.87-2.95 (1H, dd, *J* 12.8, 10.5, C*H*$_A$*H*$_B$), 3.02-3.08 (1H, dd, *J* 12.8, 2.4, C*H*$_A$*H*$_B$), 5.26-5.36 (2H, m, C*H*Me and C*H*OSi), 5.92 (1H, bd, *J* 7.0, N*H*), 7.23-7.50 (8H, m, aromatics), 7.90-7.94 (1H, m, aromatics).

To a stirred solution of the crude sulphoxide (0.444g, 0.91mmol) and sodium periodate (0.332g, 1.55mol) in acetonitrile (1cm^3) and water (1.5cm^3) was added ruthenium (III) chloride heptahydrate (0.003g). The resultant black solution was stirred at ambient temperature for 4h and then added to water (15cm^3). The aqueous phase was extracted with ethyl acetate (3 x 15cm^3) and the combined organic phases dried over

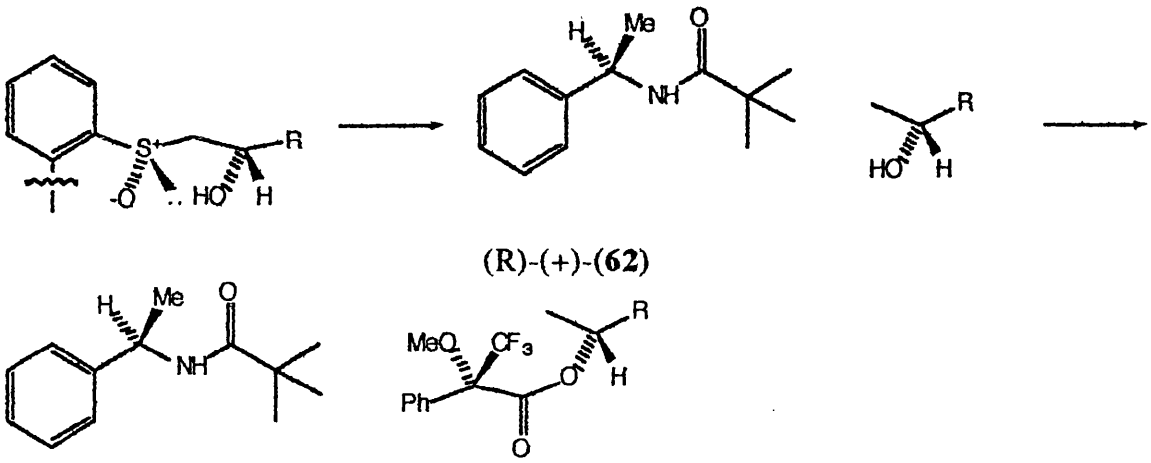
sodium sulphate. The filtrate was evaporated at reduced pressure to give (R, S)-(**109**) (0.300g, 58% from alcohol) as a white foam.

δ_H ($CDCl_3$); -0.19 (3H, s, Si*Me*), 0.12 (3H, s, Si*Me*), 0.82 (9H, s, SiC*Me*$_3$), 1.17 (9H, s, C*Me*$_3$), 1.49 (3H, d, *J* 7.0, CH*Me*), 3.90-3.99 (1H, dd, *J* 14.5, 9.0, CH_{AB}), 4.12-4.18 (1H, dd, *J* 14.5, 2.9, CH_{AB}), 5.49-5.56 (2H, m, C*H*Me and C*H*OSi), 6.09 (1H, bd, *J* 7.0, NH), 7.21-7.55 (8H, m, aromatics), 7.98-8.02 (1H, m, aromatics); m/z (F.A.B) 503 (MH^+, 10), 446 (55), 372 (100).

To an ice-cooled solution of (R, S)-(**106**) (0.097g, 0.19mmol) in tetrahydrofuran ($2.3cm^3$) was added dropwise a solution of tetrabutylammonium fluoride (1.0M in tetrahydrofuran, $0.95cm^3$, 0.95mmol). The mixture was stirred at ambient temperature for 16h and then diluted with ethyl acetate ($10cm^3$). The organic phase was washed with water ($10cm^3$) and saturated aqueous brine ($10cm^3$), dried over sodium sulphate and the resultant filtrate evaporated over reduced pressure. The methyl sulphone (R)-(**109**) (0.048g, 89%) was isolated by flash column chromatography.

δ_H ($CDCl_3$); 1.20 (9H, s, C*Me*$_3$), 1.49 (3H, d, *J* 6.8, CH*Me*), 3.48 (3H, s, SO_2*Me*), 5.57 (1H, quintet, *J* 6.8, C*H*Me), 6.30 (1H, bd, *J* 6.8, N*H*), 7.36-7.50 (2H, m, aromatics), 7.61 (1H, td, *J* 13.5, 1.5, aromatics), 8.02 (1H, dd, *J* 7.5, 1.5, aromatics); m/z (C.I.) 284 (MH^+, 100), 204 (21).

4.6.6 General method for the removal of the sulphinyl unit coupled with determination of enantiomeric excess- Raney™ reduction and (R)-(+)-MTPA ester preparation.



(R)-(+)-(**62**)

To a stirred suspension of Raney™ nickel (ex-Aldrich, 0.250g) was added a solution of the β-hydroxysulphoxide (0.025g, 0.07mmol) in tetrahydrofuran (0.6cm^3). The stirring was continued until the starting material had been consumed (as determined by t.l.c.). The suspension was filtered through a plug of silica and the residue washed with chloroform (5cm^3) and the combined organics dried over sodium sulphate. The filtrate was evaporated at reduced pressure to give a crude mixture containing the alcohol and amide (R)-(+)-(**62**) (as determined by ^{1}H NMR spectroscopy).

To a stirred chloroform (1cm^3) solution of the crude reaction mixture was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.027g, 0.12mmol) and (R)-(+)-methoxytrifluoromethylacetic acid (0.025g, 0.10mmol) and the stirring continued for 16h. The reaction mixture was filtered through a plug of celite and the residue washed with further chloroform (5cm^3). The combined organics dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure. Examination of the ^{1}H NMR (table) spectra of the crude reaction mixture furnished the required enantiomeric excesses.

Alcohol	Methyl	Methoxy	Methyne	Other
3,3-dimethylbutan-2-ol	1.19 and 1.29	3.51 and 3.56	4.85 and 4.90	0.87 and 0.90[a]
1-methyl-(2-methylbenzene) methanol	1.45 and 1.52	3.41 and 3.50	6.19 and 6.26	2.31 and 2.34[b]
1-methyl-(4-methoxybenzene) methanol	1.55 and 1.61	3.45 and 3.55	insep.	3.79 and 3.80[c]

a. *tert*-Butyl protons; b. Aromatic methyl protons; c. Aromatic methoxy.

Proton resonances from the racemic Mosher esters derived from (R)-(+)-MTPA and alcohols furnished by sodium borohydride reduction of the corresponding ketones.

Table 26

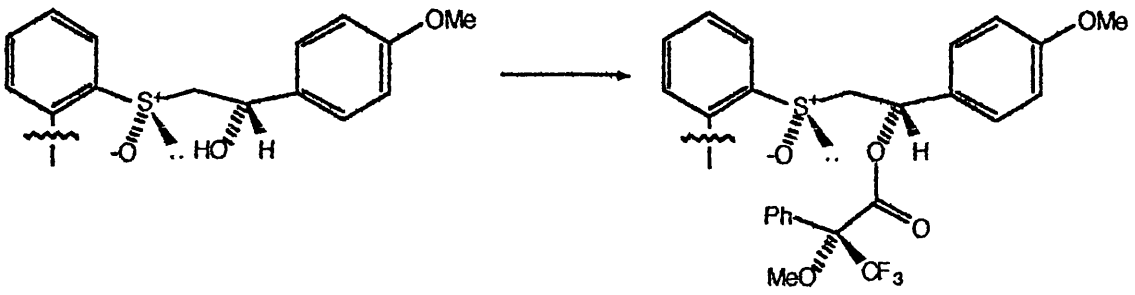
Alcohol	Methyl	Methoxy	Methyne	Other
3,3-dimethylbutan-2-ol	1.19	3.51	4.85	0.90[a]
1-methyl-(4-methoxybenzene) methanol	1.56	3.45	insep.	3.81[b]

a. *tert*-Butyl protons; b. Aromatic methoxy.

Proton resonances of the major diastereoisomer from the Mosher esters derived from (R)-(+)-MTPA and alcohols; furnished by Raney™ nickel reduction of the corresponding *cis*-β-hydroxysulphoxides.

Table 27

4.6.7 Acylation of *cis*-β-hydroxysulphoxide derived from 4-methoxyacetophenone ($S_{(S)}$ R, R)-(-)-(**110**)-check for racemisation.



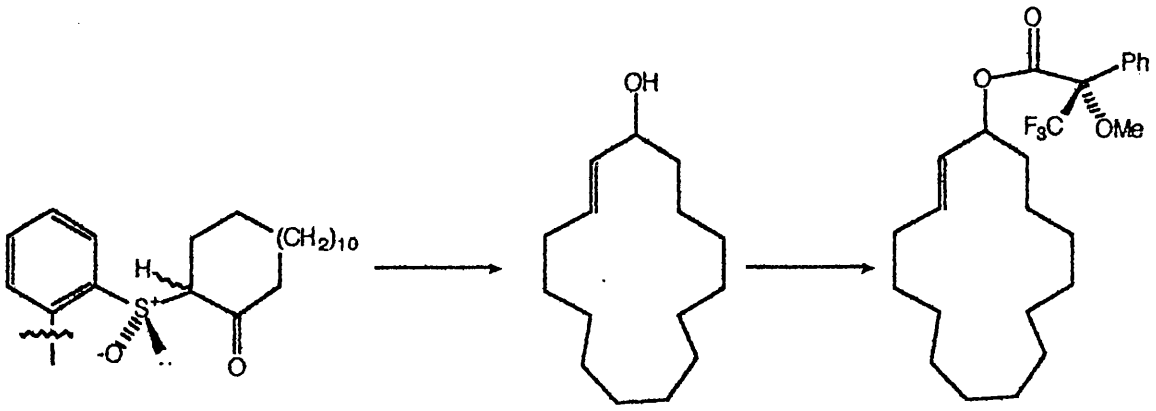
($S_{(S)}$ R, R)-(-)-(**110**) (**112**)

To a stirred solution of ($S_{(S)}$ R, R)-(-)-(**110**) (0.061g, 0.15mmol) in chloroform ($1cm^3$) was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.081g, 0.39mmol) and (R)-(+)-methoxytrifluoromethylacetic acid (0.081g, 0.35mmol). The resultant mixture was stirred at ambient temperature for 4h and then filtered and the residue washed with chloroform. The combined organics dried over anhydrous sodium sulphate, the filtrate filtered and solvent removed at reduced pressure. The residue was adsorbed onto silica and (**112**) (0.0063g, 68%) isolated by flash column chromatography (0-50% ethyl acetate petroleum ether as eluant).

δ_H ($CDCl_3$); 1.11 (9H, s, C*Me*$_3$), 1.42 (3H, d, *J* 6.7, CH*Me*), 3.41 (3H, s, O*Me*), 3.44-3.47 (1H, dd, *J* 12.5, 6.4, CH_{AB}), 3.72-3.78 (1H, dd, *J* 12.5, 7.6, CH_{AB}), 3.83 (3H, s, O*Me*), 5.24 (1H, quintet, *J* 6.7, C*H*Me), 5.86 (1H, bd, *J* 6.7, NH), 6.30 (1H, dd, *J* 7.6, 6.4, C*H*C=O), 6.91 (2H, d, *J* 8.5, aromatic), 7.29-7.73 (10H, m, aromatics), 7.45 (1H, m, aromatics).

4.7 Cyclic Ketone Chemistry - Synthesis Of Allylic Alcohols.

4.7.1 Allylic alcohol from cyclopentadecanone.



($S_{(S)}$ R)-(**95**) **(120)** **(120)**

4.7.2 Racemic allylic alcohol

To an ice-cooled solution of the cyclopentadecanone adduct ($S_{(S)}$ R)-(**95**) (0.090g, 0.19mmol) in tetrahydrofuran (4cm^3) was added in a single portion sodium borohydride (0.023g, 0.61mmol) and the resultant mixture stirred at ambient temperature for 1h. Addition of saturated aqueous ammonium chloride (10cm^3) followed by extraction with ethyl acetate (3 x 10cm^3), subsequent drying over anhydrous sodium sulphate and removal of the solvent gave the crude alcohol. The alcohol and sodium hydrogen carbonate (0.010g) were heated at 60°C in toluene (4cm^3) for 16h. The solvent was removed and the resultant crude solid adsorbed onto silica. Allylic alcohol (**120**) (0.031g, 77%) was isolated by flash column chromatography.

δ_H 0.86-0.99 (2H, m, C*H*$_2$), 0.99-1.73 (20H, m, C*H*$_2$), 1.88-2.08 (3H, m, C*H*$_2$), 4.06 (1H, m, C*H*OH), 5.39-5.45 (1H, dd, *J* 15.3, 7.65, C*H*), 5.50-5.62 (1H, m, C*H*). δ_C 24.08 (t), 25.72 (t), 26.76 (t), 26.80 (t), 26.85 (t), 26.98 (t, 2C), 27.09 (t), 27.46 (t), 28.15 (t), 31.28 (t), 36.88 (t), 73.54 (d), 133.7 (d, 2C). m/z (F. A. B) 223 (M-1$^+$, 75), 207 (100). [found m/z 223.2055 $C_{15}H_{28}O$ M-1 requires 223.2062]

Conversion to the corresponding (R)-(+)-MTPA ester (**122**) followed by examination of the ^1H NMR spectroscopic data revealed two distinct resonances for the methoxy group at 5.57 and 5.54 ppm.

4.7.3 Allylic alcohol formed *via* the diisobutylaluminium hydride/zinc bromide reduction.

To a stirred solution of the cyclopentadecanone adduct ($S_{(S)}$ R)-(**95**) (0.441g, 0.93mmol) in tetrahydofuran ($10cm^3$) at ambient temperature was added a solution of zinc bromide ($1.10cm^3$, 0.98mmol, 0.98M in tetrahydrofuran). The mixture was stirred at this temperature for 1h then cooled to -78°C. A solution of diisobutylaluminium hydride ($2.40cm^3$, 2.40mmol, 1.00M in tetrahydrofuran) was added and the resultant mixture stirred at -78°C for 1h. Quenched sequentially with methanol ($1cm^3$) and saturated aqueous ammonium chloride ($15cm^3$) and allowed to warm to ambient temperature. Sufficient aqueous hydrochloric acid (2M) was added to dissolve the white precipitate. The resultant aqueous phase was then extracted with ethyl acetate ($3x15cm^3$) and the combined organic phase washed with brine ($30cm^3$) and dried over sodium sulphate. The filtrate was evaporated at reduced pressure to furnish the crude alcohol. The crude alcohol (0.256g, 0.54mmol) and sodium hydrogen carbonate (0.045g, 0.54mmol) in toluene ($12cm^3$) were heated at 60°C for 16h. The solvent was removed and the resultant crude solid adsorbed onto silica. Allylic alcohol (-)-(**120**) (0.099g, 82%) was isolated by flash column chromatography. For spectral charcteristics see the racemic synthesis (4.7.2). $[\alpha]_D^{25}$= -20.9 (c=4.85, chloroform).

Conversion to the (R)-(+)-MTPA ester showed an enantiomeric excess of 88% with the signal at 5.54ppm corresponding to the major diastereoisomer.

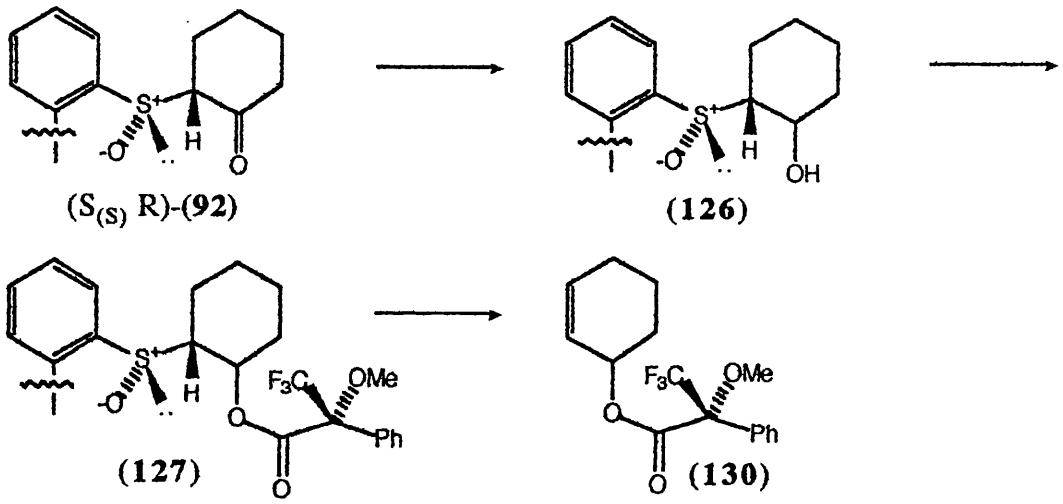
4.7.4 Allylic alcohol formed *via* the diisobutylaluminium hydride reduction.

To a stirred solution of the cyclopentadecanone adduct ($S_{(S)}$ R)-(**95**) (0.100g, 0.21mmol) in tetrahydrofuran ($1.5cm^3$) was added dropwise at -78°C a solution of

diisobutyl aluminium hydride (0.53cm^3, 0.53mmol, 1.00M in hexanes). The resulting reaction mixture was stirred at this temperature for 2h and then quenched with saturated aqueous ammonium chloride (5cm^3). The resulting mixture was treated with a few drops of aqueous hydrochloric acid (2M) and the organic phase removed. The aqueous phase was extracted with dichloromethane (3 x 5cm^3) and the combined organic extracts washed with brine, dried over sodium sulphate and the filtrate evaporated at reduced pressure to furnish the crude alcohol. The crude alcohol (0.100g, 0.21mmol) and sodium hydrogen carbonate (0.010g, 0.21mmol) in toluene (5cm^3) heated at 60°C for 16h. The solvent was removed and the resultant crude solid adsorbed onto silica. Allylic alcohol (+)-(**120**) (0.020g, 44%) and enone (0.010g, 20%) were isolated by flash column chromatography. For spectral charcteristics see the racemic synthesis. $[\alpha]_D^{25}$= +2.80 (c=1.05, chloroform).

Conversion to the (R)-(+)-MTPA ester showed an enantiomeric excess of 12% with the signal at 5.57ppm corresponding to the major diastereoisomer.

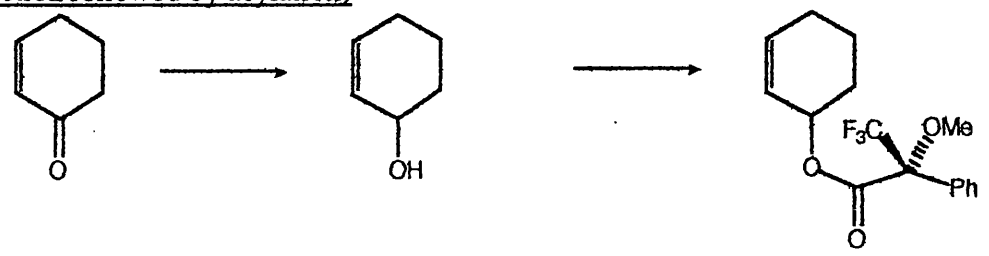
4.7.5 Synthesis of the allylic ester (**130**) based on cyclohexanone.



($S_{(S)}$ R)-(**92**) (**126**)

(**127**) (**130**)

4.7.6 Synthesis of racemic allylic ester (sodium borohydride/cerium trichloride reduction followed by acylation)



(124) (±)-**(125)** **(130)**

To an ice-cooled stirred solution of **(124)** (1.00cm^3, 10.34mmol) and cerium (III) chloride heptahydrate (4.69g, 12.6mmol) in methanol (50cm^3) was added portionwise sodium borohydride (0.435g, 11.76mmol). The mixture stirred at ambient temperature for 15m and added to a saturated aqueous solution of ammonium chloride (50cm^3) and extracted with dichloromethane (3 x 50cm^3). The combined organics dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure. Allylic alcohol (±)-(**125**) was isolated as a colourless oil (0.912g, 90%).

δ_H ($CDCl_3$); 1.51-2.05 (6H, m, CH_2), 4.17 (1H, m, CHOH), 5.71-5.75 (1H, m, CH), 5.78-5.83 (1H, m, CH).

To a stirred solution of (±)-(**125**) (0.038g, 0.39mmol) in chloroform (0.6cm^3) was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.129g, 0..63mmol) and (R)-(+)-methoxytrifluoromethylacetic acid (0.110g, 0.48mmol). The resultant mixture was stirred at ambient temperature for 4h and then filtered and the residue washed with chloroform. The combined organics dried over anhydrous sodium sulphate, the filtrate filtered and solvent removed at reduced pressure to yield crude Mosher ester (**130**).

The ^1H NMR spectrum of the racemate showed distinct resonances at 3.22 and 3.24ppm corresponding to the methoxy signal, and at 5.69-5.75 and 5.77-5.84ppm corresponding to one of the vinyl protons of each the diastereoisomers.

4.7.7 Allylic alcohol formed *via* the diisobutylaluminium hydride reduction.

To a stirred solution of the cyclohexanone adduct ($S_{(S)}$ R)-(-)-(**92**) (0.213g, 0.61mmol) in tetrahydrofuran (4.5cm^3) was added dropwise at -78°C a solution of diisobutyl aluminium hydride (1.50cm^3, 1.50mmol, 1.00M in hexanes). The resulting reaction mixture was stirred at this temperature for 2h and then quenched with saturated aqueous ammonium chloride (10cm^3). The resulting mixture was treated with a few drops of aqueous hydrochloric acid (2M) and the organic phase removed. The aqueous phase was extracted with dichloromethane (3 x 15cm^3) and the combined organic extracts washed with brine, dried over sodium sulphate and the filtrate evaporated at reduced pressure. The unreacted ($S_{(S)}$ R)-(-)-(**92**) was removed by flash column chromatography to yield (**126**) (0.067g, 31%). To a stirred solution of (**126**) (0.067g, 0.19mmol) in chloroform (1cm^3) was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.078g, 0.38mmol) and (R)-(+)-methoxytrifluoromethylacetic acid (0.079g, 0.34mmol). The resultant mixture was stirred at ambient temperature for 4h and then filtered and the residue washed with chloroform. The combined organics dried over anhydrous sodium sulphate, the filtrate filtered and solvent removed at reduced pressure to yield crude Mosher ester (**127**) (0.081g, 75%). Crude ester (**127**) (0.057g, 0.10mmol) and sodium hydrogen carbonate (0.005g, 0.10mmol) in toluene (2cm^3) are heated at reflux for 16h. The solvent was removed and the resultant crude solid adsorbed onto silica. The required allylic ester (0.036g, quantitative) (**130**) was isolated by flash column chromatography.

Examination of the ^{1}H NMR spectrum of the ester revealed only the single signal corresponding to the vinyl proton at 5.77-5.84ppm. Hence a diastereomeric ratio of >25:1 can be assigned

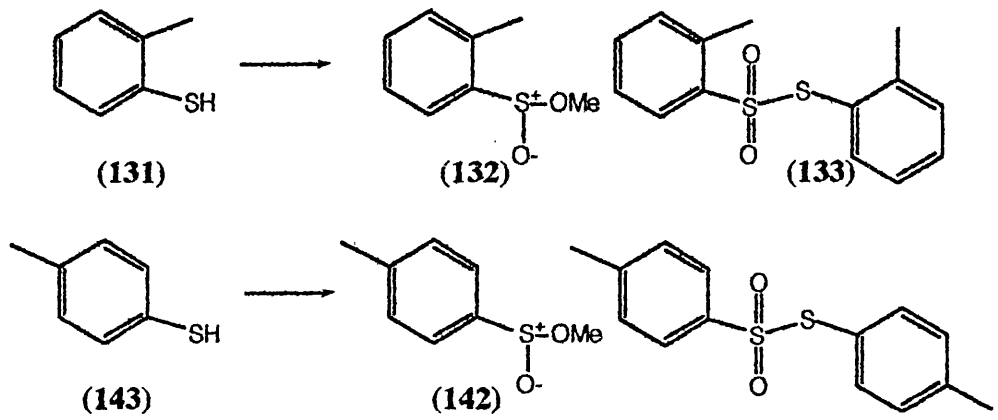
4.7.8 Allylic alcohol formed *via* the diisobutylaluminium hydride zinc (II) bromide reduction.

To a stirred solution of the cyclohexanone adduct ($S_{(S)}$ R)-(-)-(**92**) (0.213g, 0.61mmol) in tetrahydrofuran (4cm^3) and zinc (II) bromide (0.90cm^3, 0.88mmol, 0.89M in tetrahydrofuran), previously stirred at ambient temperature for 1h., was added dropwise at -78°C a solution of diisobutyl aluminium hydride (0.90cm^3, 0.90mmol, 1.00M in hexanes). The resulting reaction mixture was stirred at this temperature for 2h and then quenched with saturated aqueous ammonium chloride (10cm^3). The resulting mixture was treated with a few drops of aqueous hydrochloric acid (2M). The organic phase was then removed, the aqueous phase extracted with dichloromethane (3 x 15cm^3) and the combined organic extracts washed with brine, dried over sodium sulphate and the filtrate was evaporated at reduced pressure. The unreacted ($S_{(S)}$ R)-(-)-(**92**) was removed by flash column chromatography to yield (**126**) (0.103g, 82%). To a stirred solution of (**126**) (0.103g, 0.29mmol) in chloroform (3cm^3) was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.122g, 0.59mmol) and (R)-(+)-methoxytrifluoromethylacetic acid (0.106g, 0.45mmol). The resultant mixture was stirred at ambient temperature for 16h and then filtered and the residue washed with chloroform. The combined organics dried over anhydrous sodium sulphate, the filtrate filtered and solvent removed at reduced pressure to yield crude Mosher ester (**127**) (0.083g, 50%). The crude ester (0.083g, 0.15mmol) (**127**) and sodium hydrogen carbonate (0.008g, 0.15mmol) in toluene (3cm^3) were heated at reflux for 16h. The solvent was removed and the resultant crude solid adsorbed onto silica. The required allylic ester (**130**) (0.025g, 54%) was isolated by flash column chromatography. Examination of the ^{1}H NMR spectrum of the ester revealed signals of equal intensity at 5.69-5.75 and 5.77-5.84ppm. Hence the allylic ester was assigned as racemic.

4.8 Recycling Of The Sulphinamide

4.8.1 Model studies involving 2- and 4-thiocresol

4.8.2 Sodium periodate oxidation;



To a stirred solution of (**131**) (0.500g, 4.03mmol) in 10% aqueous methanol (17cm^3) was added in one portion sodium periodate (1.72g, 8.06mmol). The resultant dark brown reaction mixture was stirred at ambient temperature for 16h and then poured into ethyl acetate (50cm^3). The organic phase was washed with water (50cm^3) and saturated aqueous sodium thiosulphate (50cm^3), dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure. The crude mixture was columned on silica (0-25% ethyl acetate petroleum ether). The first eluted compound was thiosulphonate (**133**) (0.112g, 10%); δ_H (270 MHz) 2.15 (3H, s, *Me*), 2.69 (3H, s, *Me*), 7.05-7.55 (8H, m, aromatics). The second eluted compound was the required methyl sulphinate (**132**) (0.480g, 70%); δ_H (270 MHz) 2.48 (3H, s, *Me*), 3.47 (3H, s, *Me*), 7.22-7.28 (1H, m, aromatics), 7.38-7.48 (2H, m, aromatics), 7.90 (1H, dd, *J* 7.1, 2.0, aromatics).

For 4-thiocresol, (**143**);

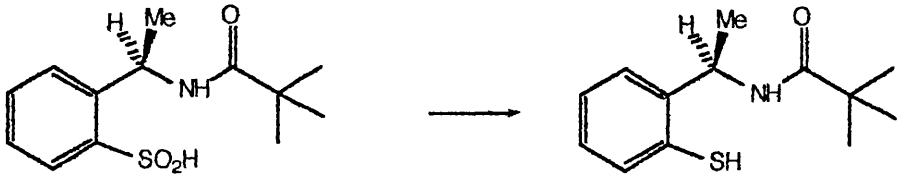
thiosulphonate (0.110g, 10%); δ_H (270 MHz) 2.38 (3H, s, *Me*), 2.42 (3H, s, *Me*), 7.11-7.30 (6H, m, aromatics), 7.46 (2H, d, *J* 8.24, aromatics).

methyl sulphinate (**142**) (0.490g, 72%); δ_H (270 MHz) 2.42 (3H, s, *Me*), 3.44 (3H, s, O*Me*), 7.35 (2H, d, *J* 8.6, aromatics), 7.59 (2H, d, *J* 8.6, aromatics).

4.8.3 Sodium periodate/iodine oxidation;

To a stirred solution of (**143**) (0.500g, 4.03mmol) and iodine (0.110g, 0.43mmol) in 10% aqueous methanol (17cm^3) was added in one portion sodium periodate (1.72g, 8.06mmol). The resultant dark brown reaction mixture was stirred at ambient temperature for 16h and then poured into ethyl acetate (50cm^3). The organic phase was washed with water (50cm^3) and saturated aqueous sodium thiosulphate (50cm^3), dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure. The crude product (0.650g, 95%) was examined by ^{1}H NMR spectroscopy to assess the purity (>95% (**142**)).

4.8.4 Synthesis of authentic sample of the thiol.



(R)-(-)-(**61**) (R)-(+)-(**70**)

To a stirred solution of (R)-(-)-(**61**) (6.43g, 23.9mmol) in toluene (75cm^3) and chloroform (75cm^3) was added, at ambient temperature, triphenylphosphine (37.6g, 143mmol) and iodine (6.17g, 24.3mmol). The mixture was vigorously stirred for 4.0h. then poured into ethyl acetate (200cm^3) and washed with water (2x200cm^3). The organic phase was dried over sodium sulphate and the filtrate evaporated at reduced pressure. Product (R)-(+)-(**70**) was isolated after column chromatography (10%-30% ethyl acetate/petroleum ether) as a white solid (5.10g, 90%).

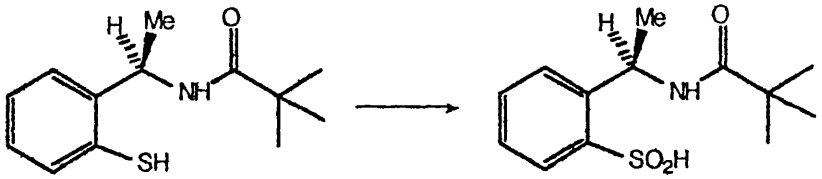
M.p 144°C (ethyl acetate/hexane).; $[\alpha]_D^{25}$ +24.4° (c=0.5, chloroform); υ_{max} (nujoll mull/cm^{-1}) 3326 and 1638; δ_H (DMSO, 270 MHz) 1.11 (9H, s, C*Me*$_3$) 1.31 (3H, d, *J* 6.7, CH*Me*) 5.05 (1H, q, *J* 6.7, C*H*Me), 5.14 (1H, s, SH), 7.15-7.02 (2H, m, aromatic H), 7.32 (2H, dd, *J* 6.1, 3.3, aromatic), 7.76 (1H, bd, *J* 6.7, NH); δ_C (DMSO) 21.27 (q) 27.37 (q), 40.22 (s), 46.21 (d), 125.5 (d), 127.0 (d), 130.3 (d), 133.6 (d), 142.9 (s), 144.3 (s), 176.5 (s); m/z (C.I.); 238(M^++1, 100), 204 (80)

(Found C, 64.6; H, 8.1; N, 5.8: $C_{13}H_{19}NOS$-0.25H_2O requires C, 64.6; H, 8.1; N, 5.8%).

As a second compound disulphide (**73**) was isolated (0.800g, 8%).

M.p. 210-212°C (ethyl acetate). υ_{max} (nujoll mull/cm^{-1}) 3357 and 1640; δ_H (270 MHz) 1.10 (18H, s, C*Me*$_3$), 1.37 (6H, d, *J* 6.75, CH*Me*), 5.25 (2H, quintet, *J* 6.75, C*H*Me), 5.98 (2H, bd, *J* 6.75, NH), 7.15 (6H, m, aromatics), 7.55 (2H, m, aromatics). δ_C 21.05 (q, 2C), 27.47 (q, 6C), 38.24 (s, 2C), 47.16 (d, 2C), 125.9 (d), 126.1 (d), 127.8 (d, 2C), 128.0 (d), 128.1 (d, 2C), 129.0 (d), 130.1 (s), 132.8 (s), 135.0 (s), 142.6 (s), 177.2 (s, 2C). m/z (F.A.B.) 473 (MH^+, 1), 441 (4), 228 (20), 206 (100). [Found C, 66.3; H, 7.87; N, 5.78: $C_{26}H_{36}N_2O_2S_2$ requires C, 66.1; H, 7.68; N, 5.93%].

4.8.5 Oxidation of thiol (R)-(+)-(**70**)with sodium periodate

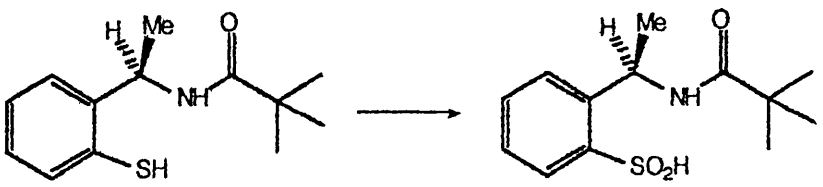


(R)-(+)-(**70**) (R)-(-)-(**61**)

To a solution of (R)-(+)-(**70**) (0.25g, 1.05mmol) in 10% aqueous methanol (8.0cm^3) was added in one portion sodium periodate (0.45g, 2.10mmol). The resultant brown suspension was heated at reflux for 16h. The reaction mixture was poured into ethyl acetate (10cm^3) and washed with water (2x10cm^3) and saturated aqueous sodium thiosulphate (10cm^3). The organic phase was dried over sodium sulphate and the filtrate evaporated at reduced pressure. The resultant oil was dissolved in tetrahydrofuran (5cm^3) and stirred vigorously with aqueous sodium hydroxide (1.0M, 5cm^3) for 1.0h. The organic solvent was removed at reduced pressure and the resulting aqueous suspension treated with concentrated hydrochloric acid until pH=1. The aqueous fraction was extracted with dichloromethane (3x5cm^3) and the combined organic phases were dried over sodium sulphate and the filtrate evaporated at reduced

pressure. (R)-(-)-(**61**) (232mg, 82%) was recovered as a white solid with identical spectral characteristics to known material.

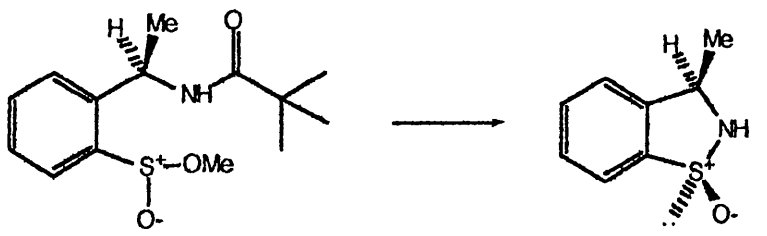
4.8.6 Oxidation of thiol (R)-(+)-(**70**) with n-bromosuccinamide and potassium carbonate



(R)-(+)-(**70**) (R)-(-)-(**61**)

To a solution of (R)-(+)-(**70**) (0.102g, 0.43mmol) in methanol (2 cm^3) at 0°C was added N-bromosuccinamide (0.226g, 1.29 mmol) and potassium carbonate (1.29mmol). The solution was stirred for 2 hours at r.t. then diluted with ethyl acetate (10 cm^3), washed with sodium bicarbonate (2 x 10cm^3) and water (10 cm^3). The organic phase was dried (sodium sulphate) and the solvent removed to give a white solid (122mg). This material was treated directly with sodium hydroxide solution (2.0M, 1 cm^3, 2 mmol) in THF (1 cm^3) for one hour at r.t. This was then acidified with 6N HCl until pH=1, extracted with dichloromethane (3 x 5cm^3) and the combined organics dried (sodium sulphate) and solvent removed to give (R)-(-)-(**61**) as a white solid (90mg, 80% from thiol).

4.8.7 Reaction of methyl sulphinate (**145**) with sodium hydride.

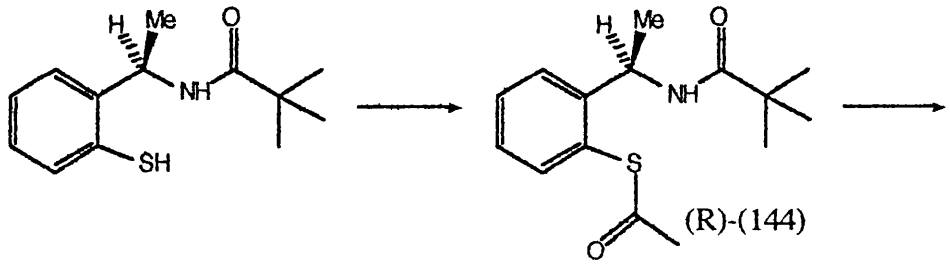


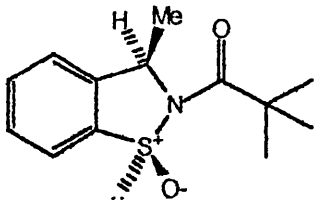
(**145**) ($S_{(S)}$ R)-(+)-*cis*-(**66**)

To a stirred solution of (**145**) (0.0465g, 0.16mmol) in tetrahydrofuran (1cm^3) was added in a single portion sodium hydride (60% dispersion in mineral oil, 0.008g,

0.20mmol). The reaction mixture was stirred at ambient temperature for 2h and quenched with saturated aqueous ammonium chloride (1cm^3) and then diluted with water (4cm^3). The aqueous was extracted with ethyl acetate (3x5cm^3) and the combined organics dried over anhydrous sodium sulphate. The filtrate was evaporated at reduced pressure to give the known ($S_{(S)}$ R)-(+)-*cis*-(**66**) (0.0207g, 77%).

4.8.8 Oxidation to sulphinamide *via* the S-acetate.





To an ice-cooled stirred solution of (R)-(+)-(**70**) (0.297g, 1.25mmol) in tetrahydrofuran (3cm^3) was added portionwise sodium hydride (60% dispersion in mineral oil, 0.056g, 1,40mmol). The resultant yellow solution was stirred at this temperature for 0.5h. To the mixture was added acetic anhydride (0.14cm^3, 1.25mmol) and stirring continued for a further 0.25h. The reaction was quenched with saturated aqueous ammonium chloride (6cm^3) and then diluted with water (5cm^3). The aqueous was extracted with dichloromethane (3x10cm^3) and the combined organics dried over anhydrous sodium sulphate. The filtrate was evaporated at reduced pressure to yield (R)-(**144**) as an orange solid (0.358g, quantitative).

υ_{max} /cm^{-1} 3303, 1706 and 1631; δ_H (DMSO, 270 MHz) 1.08 (9H, s, C*Me*$_3$), 1.24 (3H, d, *J* 7.1, CH*Me*), 3.28 (3H, s, *Me*), 5.22 (1H, quintet, *J* 7.1, C*H*Me), 7.26-7.56 (4H, m, aromatics), 7.77 (1H, bd, *J* 7.1, NH); m/z (C.I.) 280 (MH$^+$, 100), 238 (40), 204 (12).

To a stirred solution of (R)-(**144**) (0.350g, 1.25mmol) and acetic anhydride (0.132cm^3, 1.25mmol) in toluene (1cm^3) at -10°C was added dropwise a solution of sulphuryl chloride (0.21cm^3, 2.61mmol) in toluene (2cm^3). Stirring was continued for 0.8h, by which time T.L.C. showed full consumption of the starting thioacetate. The reaction was quenched with saturated aqueous ammonium chloride (6cm^3) and extracted with dichloromethane (3x10cm^3). The combined organic phases were dried over anhydrous sodium sulphate and the filtrate evaporated at reduced pressure. The ($S_{(S)}$ R)-(+)-*cis*-(**66**) was isolated by flash column chromatography (0-50% ethyl acetate petroleum ether as eluant) (0.040g, 13%). Identical spectral data to known material.

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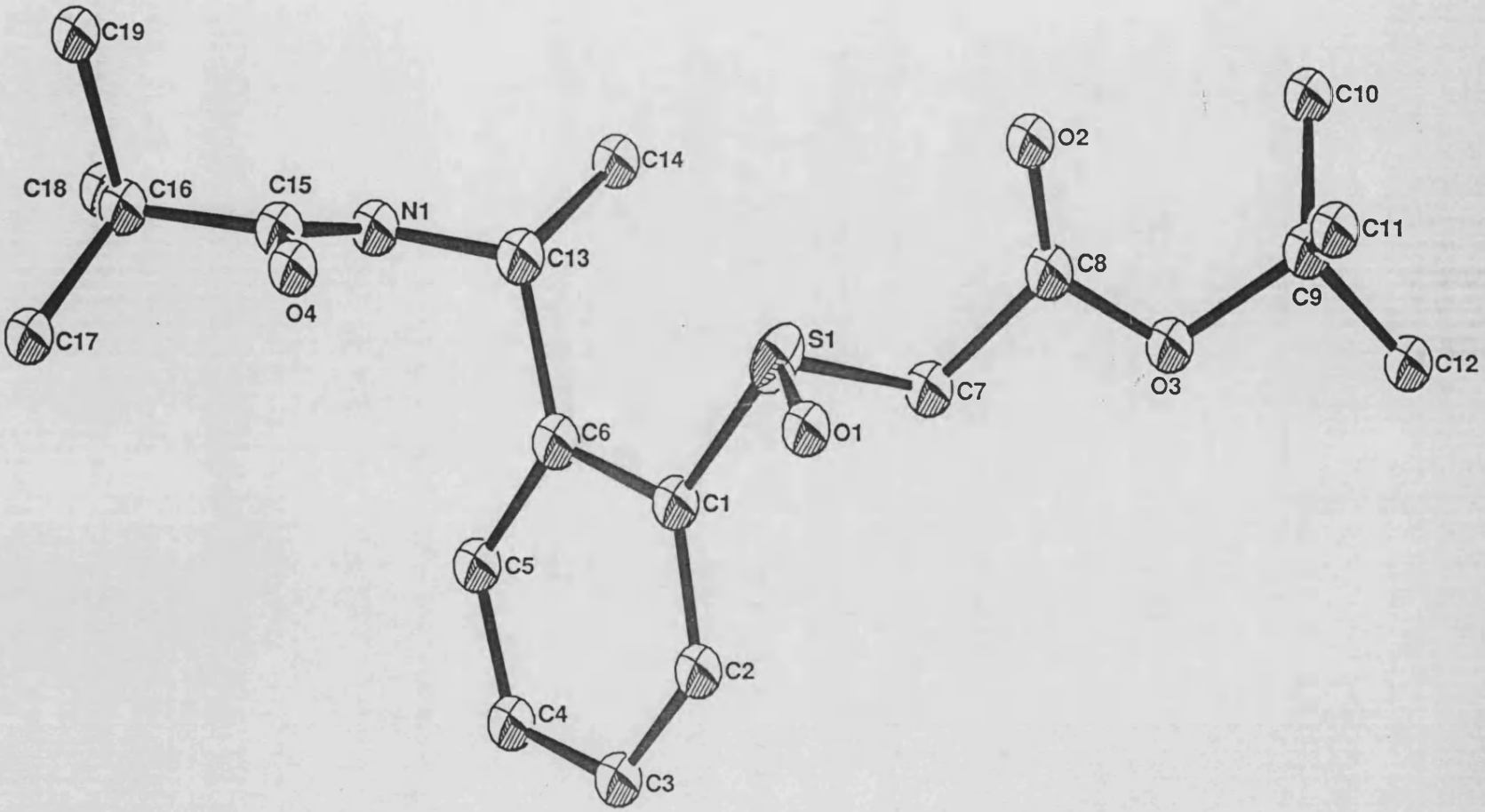
6.0 APPENDIX

6.1 X-ray Data for Sulphinyl Acetate ($S_{(S)}$ R)-(-)-(67)

A crystal of approximate dimensions 0.2 x 0.2 x 0.3 mm was used for data collection.

Crystal data: $C_{19}H_{28}O_4NS$, M = 366.5 orthrhhombic, a = 10.168(4), b = 11.497(3), c = 18.294(5)Å, U = 2138.2 Å^3, space group $P\,2_12_12_1$, Z = 4, D_c = 1.14 gcm^{-3}, μ(Mo-K$_\alpha$) = 1.53 cm^{-1}, F(000) = 788. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 22°$. 1545 reflections were collected of which 541 were unique with $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarization effects but not for adsorption. The structure was solved by direct methods and refined using the SHELX suite of programs. In the final least squares cycles the sulphur was allowed to vibrated anisotropically. All other atoms were treated isotropically. Hydrogen atoms were included at calculated position where appropriate. Final residues after 10 cycles of least squares were $R = R_w = 0.0904$, for unit weights. Max. final shift/esd was 0.005. The max. and min. residual densities were 0.11 and -0.12 eÅ^{-3} respectively. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles and given in Tables (i), (ii) and (iii) respectively. Table of anisotropic factors are available as supplementary data. The asymmetric unit is shown in Fig. II, along with the labelling scheme used.


C19
C18
C16
C15
N1
C14
C13
O4
C17
O2
C10
C8
C11
C9
S1
C12
C7
O3
O1
C6
C1
C5
C2
C4
C3

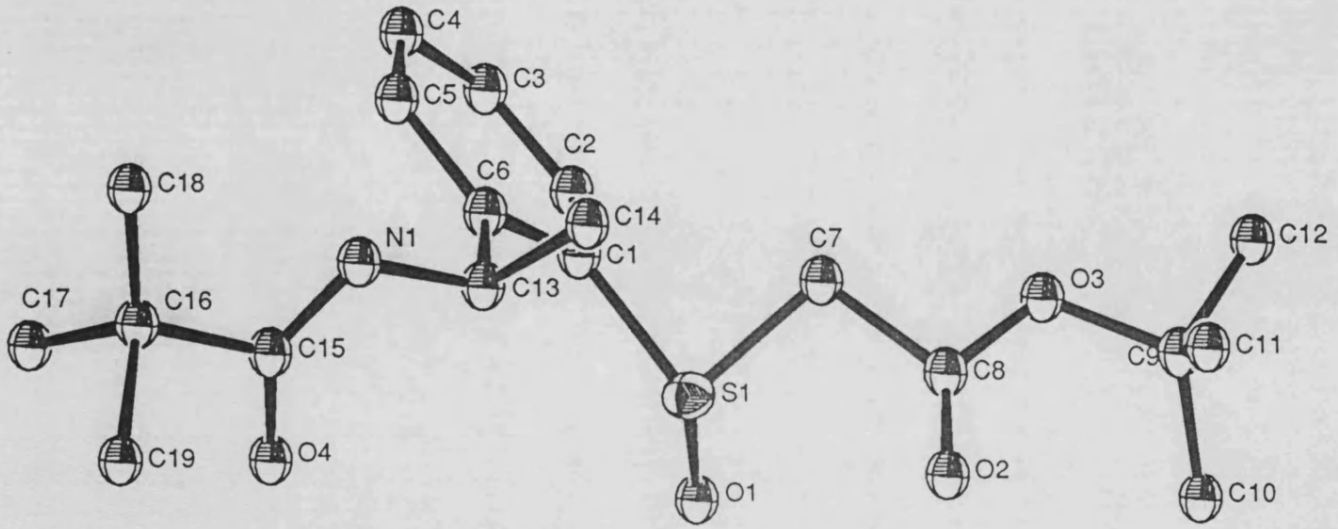

C4
C3
C5
C2
C6
C18
C14
N1
C1
C7
C12
C17
C16
C13
O3
C15
C8
C9
C11
S1
C19
O4
O2
O1
C10

TABLE 1 Fractional atomic coordinates and thermal parameters (Å) for MW5

Atom	x	y	z	Uiso or Ueq (***)	
S1	-0.2503(9)	-0.0705(5)	-0.9828(4)	0.051(4)	***
O1	-0.1503(22)	0.0052(15)	-1.0191(11)	0.068(6)	
O2	-0.2082(23)	0.0402(17)	-0.8368(12)	0.081(7)	
O3	-0.3628(21)	0.1816(16)	-0.8587(9)	0.059(6)	
O4	-0.1740(21)	-0.4396(17)	-1.0851(11)	0.069(6)	
N1	-0.3645(19)	-0.4465(15)	-1.0182(11)	0.030(5)	
C1	-0.3648(30)	-0.1187(22)	-1.0494(14)	0.045(8)	
C2	-0.4100(28)	-0.0466(23)	-1.1049(14)	0.047(8)	
C3	-0.4904(35)	-0.0839(31)	-1.1573(20)	0.090(12)	
C4	-0.5411(33)	-0.1985(24)	-1.1545(15)	0.065(10)	
C5	-0.4923(26)	-0.2734(21)	-1.1069(13)	0.037(8)	
C6	-0.4023(28)	-0.2411(21)	-1.0503(14)	0.044(8)	
C7	-0.3628(31)	0.0225(21)	-0.9383(13)	0.051(9)	
C8	-0.2932(31)	0.0836(25)	-0.8714(16)	0.059(10)	
C9	-0.3264(34)	0.2552(24)	-0.7910(17)	0.059(9)	
C10	-0.3439(39)	0.1893(29)	-0.7254(17)	0.110(14)	
C11	-0.1948(38)	0.3020(28)	-0.7960(19)	0.100(14)	
C12	-0.4267(43)	0.3458(33)	-0.7947(19)	0.127(15)	
C13	-0.3474(29)	-0.3251(18)	-0.9946(12)	0.042(7)	
C14	-0.4173(30)	-0.3113(22)	-0.9208(13)	0.052(8)	
C15	-0.2753(35)	-0.4916(22)	-1.0575(14)	0.055(9)	
C16	-0.2957(26)	-0.6192(21)	-1.0859(14)	0.038(8)	
C17	-0.2604(40)	-0.6273(27)	-1.1670(16)	0.093(11)	
C18	-0.4210(38)	-0.6735(29)	-1.0645(19)	0.111(14)	
C19	-0.1815(30)	-0.6927(24)	-1.0457(16)	0.073(10)	

TABLE 2 Fractional atomic coordinates for the hydrogen atoms

Atom	x	y	z
H21	-0.3827	0.0442	-1.1031
H31	-0.5120	-0.0262	-1.2023
H41	-0.6219	-0.2237	-1.1894
H51	-0.5142	-0.3648	-1.1134
H71	-0.4484	-0.0252	-0.9203
H72	-0.3924	0.0893	-0.9764
H101	-0.4425	0.1544	-0.7249
H102	-0.3296	0.2435	-0.6779
H103	-0.2738	0.1187	-0.7246
H111	-0.1859	0.3522	-0.8457
H112	-0.1226	0.2331	-0.7962
H113	-0.1784	0.3579	-0.7494
H121	-0.4128	0.4062	-0.7502
H122	-0.5201	0.3022	-0.7885
H123	-0.4254	0.3925	-0.8459
H131	-0.2447	-0.3017	-0.9912
H141	-0.4083	-0.2232	-0.9010
H142	-0.3700	-0.3700	-0.8829
H143	-0.5201	-0.3338	-0.9255
H171	-0.3314	-0.5801	-1.1994
H172	-0.2587	-0.7173	-1.1839
H173	-0.1641	-0.5895	-1.1746
H181	-0.5020	-0.6276	-1.0895
H182	-0.4298	-0.6686	-1.0057
H183	-0.4229	-0.7635	-1.0813
H191	-0.0868	-0.6574	-1.0606
H192	-0.1872	-0.7825	-1.0628
H193	-0.1940	-0.6876	-0.9872

TABLE 3 Anisotropic thermal parameters (A)

Atom	U11	U22	U33	U23	U13	U12
S1	0.036(5)	0.034(3)	0.082(5)	-0.005(4)	-0.004(6)	0.004(4)

TABLE 4 Bond lengths (Å)

S1	-O1	1.494(21)	S1	-C1	1.77(3)
S1	-C7	1.77(3)	O2	-C8	1.18(3)
O3	-C8	1.35(3)	O3	-C9	1.55(3)
O4	-C15	1.29(3)	N1	-C13	1.471(25)
N1	-C15	1.27(3)	C1	-C2	1.39(3)
C1	-C6	1.46(3)	C2	-C3	1.33(4)
C3	-C4	1.42(4)	C4	-C5	1.32(3)
C5	-C6	1.43(3)	C6	-C13	1.51(3)
C7	-C8	1.58(3)	C9	-C10	1.43(3)
C9	-C11	1.44(4)	C9	-C12	1.46(4)
C13	-C14	1.53(3)	C15	-C16	1.57(3)
C16	-C17	1.53(3)	C16	-C18	1.47(4)
C16	-C19	1.61(3)			

TABLE 5 Bond angles (°)

C1	-S1	-O1	109(1)	C7	-S1	-O1	107(1)
C7	-S1	-C1	95(1)	C9	-O3	-C8	118(2)
C15	-N1	-C13	118(2)	C2	-C1	-S1	122(2)
C6	-C1	-S1	119(2)	C6	-C1	-C2	119(2)
C3	-C2	-C1	122(3)	C4	-C3	-C2	120(3)
C5	-C4	-C3	120(3)	C6	-C5	-C4	123(2)
C5	-C6	-C1	115(2)	C13	-C6	-C1	121(2)
C13	-C6	-C5	124(2)	C8	-C7	-S1	110(2)
O3	-C8	-O2	130(3)	C7	-C8	-O2	124(3)
C7	-C8	-O3	106(3)	C10	-C9	-O3	111(2)
C11	-C9	-O3	112(3)	C11	-C9	-C10	111(3)
C12	-C9	-O3	101(3)	C12	-C9	-C10	109(3)
C12	-C9	-C11	112(3)	C6	-C13	-N1	111(2)
C14	-C13	-N1	107(2)	C14	-C13	-C6	111(2)
N1	-C15	-O4	127(2)	C16	-C15	-O4	114(2)
C16	-C15	-N1	118(3)	C17	-C16	-C15	110(2)
C18	-C16	-C15	115(3)	C18	-C16	-C17	116(3)
C19	-C16	-C15	104(2)	C19	-C16	-C17	104(2)
C19	-C16	-C18	106(2)				

TABLE 6 Intermolecular distances (Å)

O1	...H192	2.60	1	0.0	-1.0	0.0
O1	...H143	2.58	4	-1.0	-1.0	-2.0
O1	...H181	2.86	4	-1.0	-1.0	-2.0
O1	...H182	2.96	4	-1.0	-1.0	-2.0
O2	...H51	2.96	4	-1.0	-1.0	-2.0
O2	...H181	2.69	4	-1.0	-1.0	-2.0
O3	...H191	2.73	4	0.0	-1.0	-2.0
O4	...H102	2.82	3	-1.0	0.0	0.0
O4	...H71	2.33	4	-1.0	-1.0	-2.0
C2	...H103	2.99	3	-1.0	0.0	0.0
C3	...H103	2.98	3	-1.0	0.0	0.0
C7	...H191	2.76	4	0.0	-1.0	-2.0

TABLE 7 Intramolecular distances (Å)

S1	...O2	2.99	S1	...C2	2.78
S1	...H21	2.90	S1	...C6	2.78
S1	...H71	2.37	S1	...H72	2.34
S1	...C8	2.73	S1	...H131	2.66
S1	...H141	2.81	O1	...C1	2.66
O1	...H21	2.85	O1	...C7	2.63
O1	...H72	2.76	O2	...O3	2.30
O2	...C7	2.44	O2	...H71	2.98
O2	...C9	2.87	O2	...C10	3.00
O2	...H103	2.34	O2	...H112	2.49
O3	...C7	2.34	O3	...H71	2.77
O3	...H72	2.42	O3	...C10	2.45
O3	...H101	2.60	O3	...H103	2.71
O3	...C11	2.48	O3	...H111	2.67
O3	...H112	2.76	O3	...C12	2.31
O3	...H122	2.48	O3	...H123	2.52
O4	...N1	2.29	O4	...C13	2.75
O4	...H131	2.45	O4	...C16	2.41
O4	...C17	2.77	O4	...H173	2.38
O4	...C19	3.00	O4	...H191	2.69
N1	...C5	2.88	N1	...H51	2.50
N1	...C6	2.46	N1	...H131	2.12
N1	...C14	2.42	N1	...H142	2.63
N1	...H143	2.65	N1	...C16	2.44
N1	...C18	2.80	N1	...H181	2.83
N1	...H182	2.65	C1	...H21	2.12
C1	...C3	2.39	C1	...C4	2.78
C1	...C5	2.44	C1	...C7	2.60
C1	...H71	2.73	C1	...H72	2.75

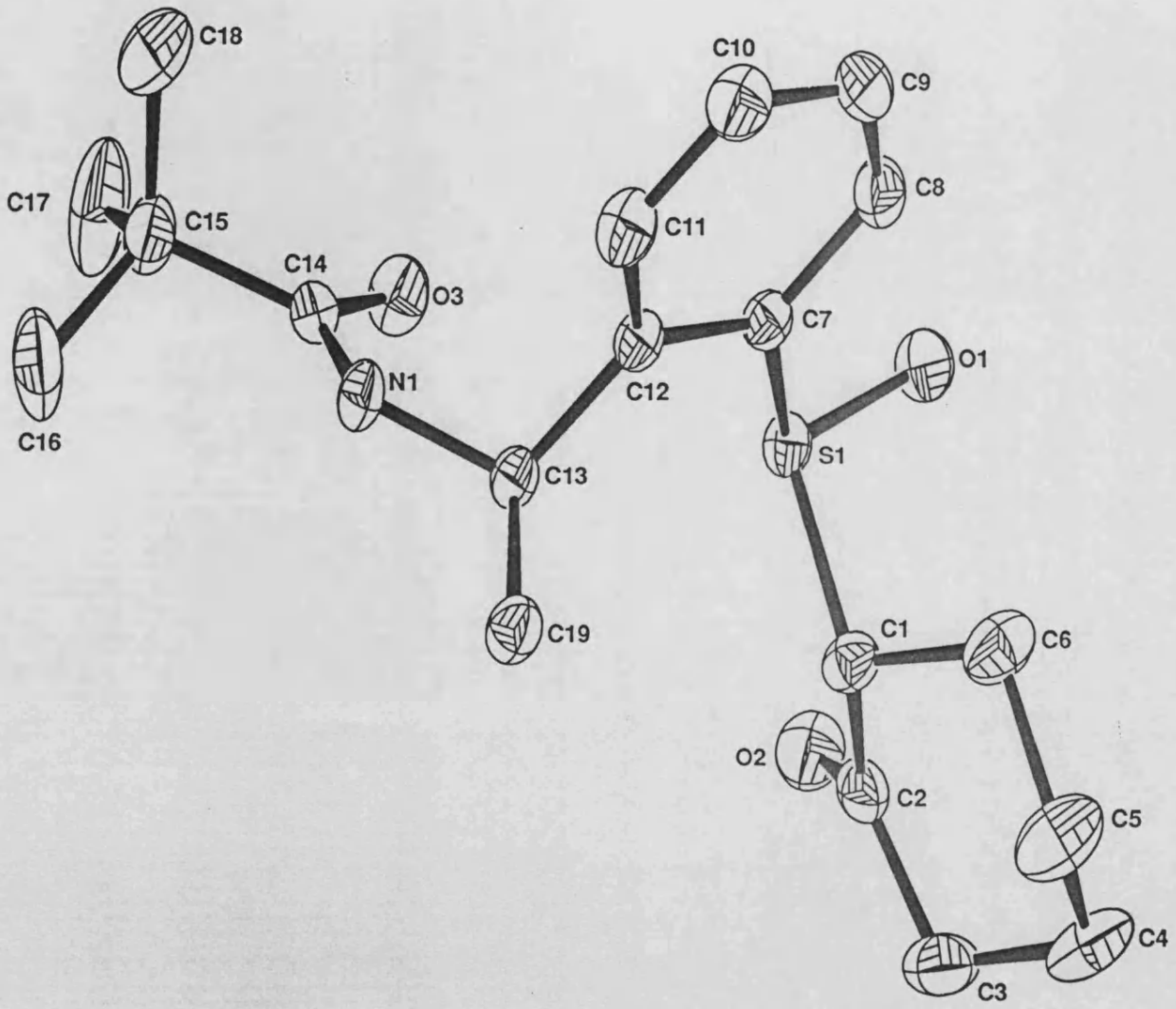
C1	...C13	2.58	C1	...H131	2.66
C2	...H31	2.07	C2	...C4	2.38
C2	...C5	2.74	C2	...C6	2.45
C2	...H72	2.83	H21	...C3	2.09
C3	...H41	2.17	C3	...C5	2.36
C3	...C6	2.81	H31	...C4	2.19
C4	...H51	2.07	C4	...C6	2.42
H41	...C5	2.08	C5	...C13	2.60
H51	...C6	2.16	H51	...C13	2.80
C6	...H131	2.06	C6	...C14	2.51
C6	...H141	2.74	C6	...H143	2.79
C7	...H141	2.94	H71	...C8	2.20
H72	...C8	2.17	C8	...C9	2.48
C8	...C10	2.98	C8	...H103	2.72
C8	...H112	2.80	C9	...H101	2.05
C9	...H102	2.07	C9	...H103	2.06
C9	...H111	2.07	C9	...H112	2.09
C9	...H113	2.06	C9	...H121	2.08
C9	...H122	2.04	C9	...H123	2.12
C10	...C11	2.38	C10	...H112	2.64
C10	...H113	2.60	C10	...C12	2.36
C10	...H121	2.63	C10	...H122	2.49
H101	...C12	2.55	H102	...C11	2.65
H102	...C12	2.63	H103	...C11	2.61
C11	...C12	2.41	C11	...H121	2.66
C11	...H123	2.72	H111	...C12	2.62
H113	...C12	2.66	C13	...H141	2.17
C13	...H142	2.12	C13	...H143	2.17
C13	...C15	2.35	H131	...C14	2.18
H131	...C15	2.52	C15	...C17	2.54
C15	...H171	2.85	C15	...H173	2.67

C15 ...C18	2.57	C15 ...H181	2.85
C15 ...H182	2.74	C15 ...C19	2.51
C15 ...H191	2.70	C15 ...H193	2.72
C16 ...H171	2.15	C16 ...H172	2.15
C16 ...H173	2.13	C16 ...H181	2.10
C16 ...H182	2.08	C16 ...H183	2.10
C16 ...H191	2.22	C16 ...H192	2.22
C16 ...H193	2.22	C17 ...C18	2.54
C17 ...H181	2.84	C17 ...H183	2.76
C17 ...C19	2.48	C17 ...H191	2.65
C17 ...H192	2.71	H171...C18	2.84
H172...C18	2.78	H172...C19	2.66
H173...C19	2.65	C18 ...C19	2.47
C18 ...H192	2.69	C18 ...H193	2.71
H182...C19	2.64	H183...C19	2.67

6.2 X-ray Data for Cyclohexanone Adduct (92).

A crystal of approximate dimensions 0.2 x 0.2 x 0.2 mm was used for data collection.

Crystal data: $C_{20}H_{29}O_3NSCl_2$, M = 434.4 triclinic, a = 8.106(1), b = 8.8.01(2), c = 9.611(2)Å, $\underline{\alpha}$ = 112.39(2), $\underline{\beta}$ = 102.71(2), $\underline{\gamma}$ = 103.49(2), U = 578.9 Å^3, space group P 1, Z = 1, D_c = 1.24 gcm^{-3}, μ(Mo-K$_\alpha$) = 3.41 cm^{-1}, F(000) = 230. Data were measured at room temperature on a CAD4 four-circle diffractometer in the range $2 \leq \theta \leq 26°$. 2432 reflections were collected of which 2118 were unique with $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarization effects but not for adsorption. The structure was solved by direct methods and refined using the SHELX suite of programs. In the final least squares cycles all atoms were allowed to vibrated anisotropically. All other atoms were treated isotropically. Hydrogen atoms were included at calculated position except in the case of N1, where the hydrogen was located in an advanced Fourier and refined at a fixed distance from the parent atom. Examination of the overall packing arrangement revealed that molecules are linked in 1-dimensional array along x, by intermolecular hydrogen bonds between N1 and O1, and O1 and N1 of molecules generated by the operators x-1, y, z, and x+1, y, z respectively. Final residues after 12 cycles of least squares were $R = R_w = 0.0493$, for unit weights. Max. final shift/esd was 0.005. The max. and min. residual densities were 0.20 and -0.15 eÅ^{-3} respectively. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles and given in Tables (i), (ii) and (iii) respectively. Table of anisotropic factors are available as supplementary data. The asymmetric unit is shown in Fig. I, along with the labelling scheme used.


C18
C10
C9
C17
C15
C8
C11
C14
O3
C7
O1
C12
N1
C16
S1
C13
C19
C1
C6
O2
C2
C5
C4
C3

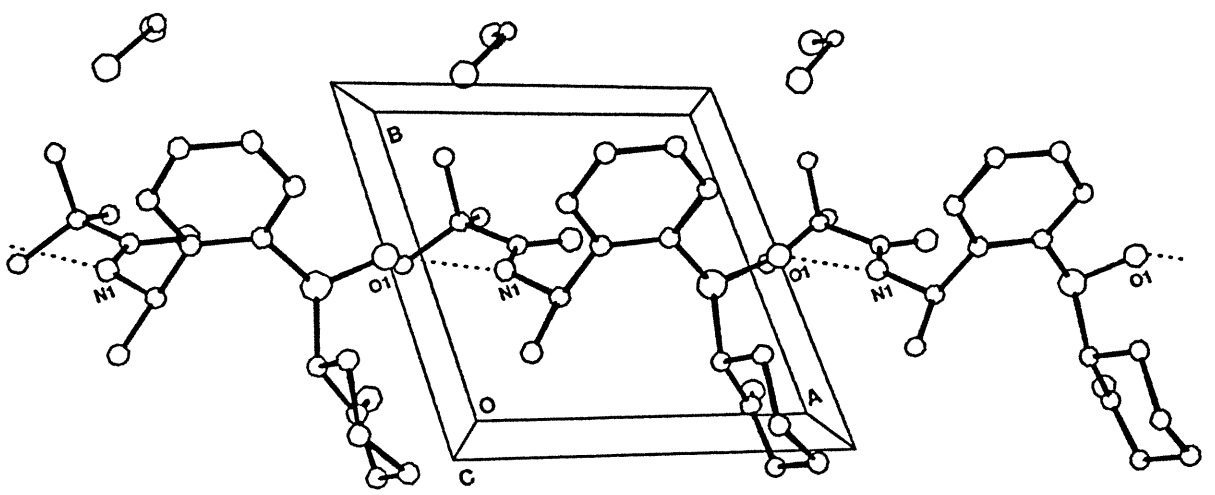

B
O
A
C
N1
O1
N1
O1
N1
O1

TABLE 1 Fractional atomic coordinates and thermal parameters (Å) for 93MW1

Atom	x	y	z	Uiso or Ueq	(***)
S1	-0.20300	-0.55750	-0.03440	0.0405(7)	***
O1	0.0001(6)	-0.4785(6)	0.0280(5)	0.053(2)	***
O2	-0.1900(8)	-0.8654(7)	-0.2586(6)	0.069(3)	***
O3	-0.5278(6)	-0.4315(6)	-0.2412(6)	0.064(3)	***
N1	-0.7241(6)	-0.5177(7)	-0.1326(6)	0.047(3)	***
C1	-0.2569(8)	-0.7643(7)	-0.0172(7)	0.048(3)	***
C2	-0.2164(8)	-0.8955(8)	-0.1522(8)	0.045(3)	***
C3	-0.2137(11)	-1.0578(9)	-0.1430(10)	0.070(5)	***
C4	-0.1121(14)	-1.0277(11)	0.0262(12)	0.100(6)	***
C5	-0.1833(14)	-0.9196(11)	0.1474(11)	0.103(7)	***
C6	-0.1553(12)	-0.7389(9)	0.1491(9)	0.072(5)	***
C7	-0.2753(8)	-0.4303(7)	0.1226(7)	0.040(3)	***
C8	-0.1389(9)	-0.3014(8)	0.2652(7)	0.048(4)	***
C9	-0.1881(11)	-0.1941(9)	0.3849(7)	0.054(4)	***
C10	-0.3658(11)	-0.2116(10)	0.3617(8)	0.063(4)	***
C11	-0.5002(9)	-0.3380(9)	0.2194(7)	0.058(4)	***
C12	-0.4570(8)	-0.4508(7)	0.0951(6)	0.040(3)	***
C13	-0.6068(7)	-0.5899(7)	-0.0594(7)	0.043(3)	***
C14	-0.6734(8)	-0.4466(8)	-0.2233(7)	0.040(3)	***
C15	-0.8085(9)	-0.3800(9)	-0.3023(9)	0.063(4)	***
C16	-0.7581(13)	-0.3638(16)	-0.4445(13)	0.141(9)	***
C17	-1.0034(10)	-0.5045(14)	-0.3644(12)	0.101(7)	***
C18	-0.7874(17)	-0.1992(13)	-0.1727(15)	0.134(10)	***
C19	-0.7245(9)	-0.7342(8)	-0.0307(8)	0.056(4)	***
C20	-0.4941(12)	0.2250(12)	-0.4938(10)	0.089(6)	***
Cl1	-0.6648(6)	0.0796(5)	-0.4771(5)	0.141(3)	***
Cl2	-0.5433(8)	0.2312(10)	-0.6706(5)	0.293(6)	***
H1	-0.8226(73)	-0.5021(**)	-0.0958(91)	0.096(5)	

TABLE 2 Fractional atomic coordinates for the hydrogen atoms

Atom	x	y	z
H11	-0.3973	-0.8136	-0.0300
H31	-0.3515	-1.1433	-0.1807
H32	-0.1490	-1.1205	-0.2235
H41	0.0302	-0.9589	0.0584
H42	-0.1312	-1.1531	0.0268
H51	-0.3257	-0.9880	0.1150
H52	-0.1118	-0.9009	0.2651
H61	-0.0129	-0.6704	0.1813
H62	-0.2060	-0.6627	0.2357
H81	0.0014	-0.2857	0.2818
H91	-0.0854	-0.0959	0.4976
H101	-0.4015	-0.1256	0.4555
H111	-0.6395	-0.3503	0.2037
H131	-0.5400	-0.6460	-0.1409
H161	-0.8506	-0.3173	-0.5020
H162	-0.7669	-0.4907	-0.5301
H163	-0.6219	-0.2721	-0.4003
H171	-1.0181	-0.6310	-0.4550
H172	-1.0929	-0.4511	-0.4154
H173	-1.0370	-0.5192	-0.2664
H181	-0.8796	-0.1474	-0.2228
H182	-0.6504	-0.1104	-0.1314
H183	-0.8173	-0.2134	-0.0732
H191	-0.6392	-0.7888	0.0234
H192	-0.8227	-0.8369	-0.1437
H193	-0.7935	-0.6773	0.0482
H201	-0.3762	0.1877	-0.4768
H202	-0.4641	0.3550	-0.4003

TABLE 3 Anisotropic thermal parameters (Å)

Atom	U11	U22	U33	U23	U13	U12
S1	0.035(1)	0.046(1)	0.040(1)	0.020(1)	0.018(1)	0.020(1)
O1	0.037(2)	0.056(2)	0.065(3)	0.028(2)	0.025(2)	0.018(2)
O2	0.087(4)	0.067(3)	0.053(3)	0.015(2)	0.026(3)	0.040(3)
O3	0.046(3)	0.071(3)	0.074(3)	0.046(3)	0.028(2)	0.024(2)
N1	0.035(3)	0.055(3)	0.052(3)	0.032(2)	0.018(2)	0.024(2)
C1	0.044(3)	0.042(3)	0.059(4)	0.027(3)	0.025(3)	0.020(3)
C2	0.034(3)	0.045(3)	0.058(4)	0.013(3)	0.009(3)	0.014(3)
C3	0.072(5)	0.041(4)	0.096(6)	0.021(4)	0.031(5)	0.020(4)
C4	0.112(7)	0.060(5)	0.127(8)	0.061(5)	0.064(6)	0.050(5)
C5	0.121(7)	0.084(6)	0.104(7)	0.072(6)	0.067(6)	0.052(6)
C6	0.097(6)	0.061(4)	0.058(4)	0.035(4)	0.037(4)	0.042(4)
C7	0.043(3)	0.038(3)	0.038(3)	0.018(2)	0.017(2)	0.019(3)
C8	0.051(4)	0.052(4)	0.043(3)	0.019(3)	0.009(3)	0.021(3)
C9	0.070(5)	0.053(4)	0.041(4)	0.010(3)	0.001(3)	0.020(4)
C10	0.083(5)	0.062(4)	0.045(4)	0.015(3)	0.026(4)	0.040(4)
C11	0.059(4)	0.064(4)	0.053(4)	0.027(3)	0.032(3)	0.037(3)
C12	0.042(3)	0.042(3)	0.038(3)	0.021(2)	0.018(2)	0.021(3)
C13	0.037(3)	0.045(3)	0.046(3)	0.023(3)	0.018(3)	0.021(3)
C14	0.036(3)	0.041(3)	0.044(3)	0.018(3)	0.008(2)	0.012(2)
C15	0.048(4)	0.068(4)	0.071(4)	0.045(4)	0.013(3)	0.023(3)
C16	0.079(6)	0.206(12)	0.139(9)	0.142(10)	0.046(6)	0.067(7)
C17	0.043(4)	0.137(8)	0.124(8)	0.093(7)	-0.006(5)	0.012(5)
C18	0.132(10)	0.081(7)	0.189(13)	0.026(7)	-0.017(9)	0.072(7)
C19	0.045(3)	0.054(4)	0.071(4)	0.038(3)	0.023(3)	0.019(3)
C20	0.086(6)	0.102(7)	0.077(6)	0.048(5)	0.032(5)	0.038(5)
C11	0.146(3)	0.107(2)	0.171(3)	0.016(2)	0.083(3)	-0.010(2)
C12	0.225(5)	0.529(11)	0.126(3)	0.200(5)	0.094(3)	0.193(6)

TABLE 4 Bond lengths (Å)

S1	-O1	1.506(4)	S1	-C1	1.850(6)
S1	-C7	1.811(5)	O2	-C2	1.199(8)
O3	-C14	1.214(7)	N1	-C13	1.460(7)
N1	-C14	1.332(7)	N1	-H1	0.959(10)
C1	-C2	1.532(8)	C1	-C6	1.531(9)
C2	-C3	1.469(9)	C3	-C4	1.542(11)
C4	-C5	1.517(11)	C5	-C6	1.547(9)
C7	-C8	1.397(8)	C7	-C12	1.393(8)
C8	-C9	1.388(9)	C9	-C10	1.371(10)
C10	-C11	1.383(9)	C11	-C12	1.406(7)
C12	-C13	1.519(8)	C13	-C19	1.555(8)
C14	-C15	1.547(8)	C15	-C16	1.556(10)
C15	-C17	1.527(10)	C15	-C18	1.543(11)
C20	-C11	1.733(9)	C20	-C12	1.684(8)

TABLE 5 Bond angles (°)

C1	-S1	-O1	105.5(3)	C7	-S1	-O1	105.8(2)
C7	-S1	-C1	99.0(3)	C14	-N1	-C13	119.5(5)
H1	-N1	-C13	118(5)	H1	-N1	-C14	122(5)
C2	-C1	-S1	106.4(4)	C6	-C1	-S1	112.6(4)
C6	-C1	-C2	113.2(5)	C1	-C2	-O2	121.0(6)
C3	-C2	-O2	123.0(6)	C3	-C2	-C1	116.0(6)
C4	-C3	-C2	113.7(6)	C5	-C4	-C3	110.3(7)
C6	-C5	-C4	109.8(6)	C5	-C6	-C1	109.8(6)
C8	-C7	-S1	116.5(4)	C12	-C7	-S1	120.9(4)
C12	-C7	-C8	122.4(5)	C9	-C8	-C7	118.3(6)
C10	-C9	-C8	120.6(6)	C11	-C10	-C9	120.8(6)
C12	-C11	-C10	120.6(6)	C11	-C12	-C7	117.2(5)
C13	-C12	-C7	123.0(5)	C13	-C12	-C11	119.8(5)
C12	-C13	-N1	112.9(4)	C19	-C13	-N1	108.8(5)
C19	-C13	-C12	110.9(5)	N1	-C14	-O3	122.2(5)
C15	-C14	-O3	121.4(6)	C15	-C14	-N1	116.4(5)
C16	-C15	-C14	107.9(6)	C17	-C15	-C14	112.0(6)
C17	-C15	-C16	109.4(7)	C18	-C15	-C14	106.9(6)
C18	-C15	-C16	111.1(8)	C18	-C15	-C17	109.5(8)
C12	-C20	-C11	114.9(6)				

TABLE 6 Intermolecular distances (Å)

S1	...H173	2.93	1	-1.0	0.0	0.0
O1	...N1	2.99	1	-1.0	0.0	0.0
O1	...H111	2.74	1	-1.0	0.0	0.0
O1	...H173	2.65	1	-1.0	0.0	0.0
O1	...H193	2.72	1	-1.0	0.0	0.0
O1	...H1	2.06	1	-1.0	0.0	0.0
O2	...H91	2.90	1	0.0	1.0	1.0
O2	...H101	2.65	1	0.0	1.0	1.0
O2	...H192	2.85	1	-1.0	0.0	0.0
O2	...H201	2.56	1	0.0	1.0	0.0
O3	...H31	2.37	1	0.0	-1.0	0.0
O3	...H202	2.18	1	0.0	1.0	0.0
H41	...C19	2.97	1	-1.0	0.0	0.0
C8	...H161	2.93	1	-1.0	0.0	-1.0
H131	...C11	2.96	1	0.0	1.0	0.0
H191	...C12	2.80	1	0.0	1.0	-1.0

TABLE 7 Intramolecular distances (Å)

S1	...O2	2.79	S1	...H11	2.45
S1	...C2	2.72	S1	...C6	2.82
S1	...H61	2.92	S1	...C8	2.74
S1	...H81	2.85	S1	...C12	2.79
S1	...H131	2.51	O1	...C1	2.68
O1	...H61	2.63	O1	...C7	2.65
O1	...C8	2.85	O1	...H81	2.38
O2	...C1	2.38	O2	...C3	2.35
O2	...H31	2.93	O2	...H32	2.48
O3	...N1	2.23	O3	...C13	2.71
O3	...H131	2.42	O3	...C15	2.41
O3	...C16	2.73	O3	...H162	2.79
O3	...H163	2.55	N1	...H111	2.83
N1	...C12	2.48	N1	...H131	2.07
N1	...C15	2.45	N1	...C17	2.86
N1	...H173	2.57	N1	...H183	2.84
N1	...C19	2.45	N1	...H192	2.69
N1	...H193	2.69	C1	...C3	2.55
C1	...H31	2.91	C1	...C4	2.95
C1	...C5	2.52	C1	...H51	2.74
C1	...H61	2.15	C1	...H62	2.15
C1	...C7	2.78	C1	...H131	2.94
H11	...C2	2.16	H11	...C3	2.90
H11	...C5	2.73	H11	...C6	2.07
H11	...C7	2.92	H11	...C13	2.94
H11	...C19	2.90	C2	...H31	2.08
C2	...H32	2.08	C2	...C4	2.52
C2	...H41	2.83	C2	...C5	2.93
C2	...C6	2.56	C2	...H61	2.87

C3 ...H41	2.15	C3 ...H42	2.15
C3 ...C5	2.51	C3 ...H51	2.73
C3 ...C6	2.96	H31 ...C4	2.14
H31 ...C5	2.79	H32 ...C4	2.14
C4 ...H51	2.13	C4 ...H52	2.14
C4 ...C6	2.51	C4 ...H61	2.73
H41 ...C5	2.13	H41 ...C6	2.72
H42 ...C5	2.13	C5 ...H61	2.16
C5 ...H62	2.16	H51 ...C6	2.16
H52 ...C6	2.16	H62 ...C7	2.76
H62 ...C8	2.99	C7 ...H81	2.16
C7 ...C9	2.39	C7 ...C10	2.75
C7 ...C11	2.39	C7 ...C13	2.56
C7 ...H131	2.58	C8 ...H91	2.14
C8 ...C10	2.40	C8 ...C11	2.79
C8 ...C12	2.44	H81 ...C9	2.15
C9 ...H101	2.12	C9 ...C11	2.40
C9 ...C12	2.80	H91 ...C10	2.12
C10 ...H111	2.14	C10 ...C12	2.42
H101...C11	2.13	C11 ...C13	2.53
C11 ...H193	2.91	H111...C12	2.16
H111...C13	2.72	H111...H1	2.56
C12 ...H131	2.09	C12 ...C19	2.53
C12 ...H191	2.73	C12 ...H193	2.80
C12 ...H1	2.95	C13 ...C14	2.41
C13 ...H191	2.17	C13 ...H192	2.17
C13 ...H193	2.17	C13 ...H1	2.09
H131...C14	2.54	H131...C19	2.18
C14 ...C16	2.51	C14 ...H162	2.73
C14 ...H163	2.73	C14 ...C17	2.55
C14 ...H171	2.79	C14 ...H173	2.77

C14 ...C18	2.48	C14 ...H182	2.69
C14 ...H183	2.69	C14 ...H1	2.01
C15 ...H161	2.17	C15 ...H162	2.17
C15 ...H163	2.17	C15 ...H171	2.15
C15 ...H172	2.14	C15 ...H173	2.14
C15 ...H181	2.16	C15 ...H182	2.16
C15 ...H183	2.16	C15 ...H1	2.60
C16 ...C17	2.52	C16 ...H171	2.72
C16 ...H172	2.75	C16 ...C18	2.56
C16 ...H181	2.80	C16 ...H182	2.76
H161...C17	2.73	H161...C18	2.81
H162...C17	2.76	H163...C18	2.76
C17 ...C18	2.51	C17 ...H181	2.72
C17 ...H183	2.75	C17 ...H1	2.66
H172...C18	2.73	H173...C18	2.73
H173...H1	2.04	C18 ...H1	2.99
H183...H1	2.46	C19 ...H1	2.59
H193...H1	2.45	H201...C11	2.31
H201...C12	2.27	H202...C11	2.31
H202...C12	2.27	C11 ...C12	2.88